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 In an earlier unpublished study, we had shown that the erythropoietin levels were low in these infants.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 (55%) 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 (HIVDVG) and phototherapy, with phototherapy alone demonstrated that significantly fewer infants required exchange transfusion in the HIVDVG 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 negative direct antiglobulin test. Anti-D antibodies were now detected in the patient’s serum; these were not present in her mother whose antibody screen was negative and whose blood group was A Rhessus D positive. The manufacturer of the IVIG investigated the batches 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.

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 (HIVDVG) in cases of haemolytic disease of newborns (HDN) with their conclusion showing the effectiveness of HIVDVG. I have the following observations to make with respect to the 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 enterohepatic 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, isbagol husk and so forth, and further reduce serum bilirubin levels. Further randomised controlled trials are required before administration of HIVDVG becomes routine in HDN. These trials should compare use of current effective phototherapy combinations with the...
highest possible irradiance, agents that de-
crease enterohepatic recirculation of bilirubin
with or without HDIVIG, and the need for
exchange transfusion in HDN. They should
also address cost effectiveness and safety,
considering the cost of HDIVIG in the develop-
ing world.

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hyperbilirubinemia in rhesus hemolytic

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
receive intravenous immunoglobulin (IVIG), as is also demonstrated in our system-
etic review. Even when infants have received exchange transfusions (XTs) top up red cell
transfusions may be required. In a recent local audit of XTs, 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 34 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)
and its use in this situation. 2
We await with interest the outcome of a Cochrane meta-analysis of this therapy in
newborn infants (currently at the protocol
stage).

We reviewed our computer database for a three year period from December 1999 to
December 2002 to postulate what impact IVIG might have on our population of babies with
haemolytic disease of the newborn. Two hun-
dred and five babies had a positive direct
Combs test (DCT) result. Of these infants, 12
received XTs. There is a degree of under ascer-
tainment with this database as there were
four additional babies who required an XT
during this time period. However, we make
the assumption that the proportions of those
missed requiring XTs is similar to the propor-
tions of DCT positive babies who were missed
from the database. Eighty five babies had
moderate or strongly positive DCT. Of these 11
received an XT, giving an XT rate in this group
of 13%. After IVIG, the relative risk of requir-
ing an XT is 0.28, thus with IVIG the XT rate
would be reduced to 3.6%, decreasing the
number of XTs to three and therefore prevent-
ing eight. If IVIG were administered to all babies with moderate or strongly positive
DCT, in our population the number needed to
treat would be 10.6 to prevent one XT. The
degree of positivity of the DCT is an objective
validated assessment of the strength of
antibody/antibody reaction, determined by
the degree of agglutination in the laboratory. 3
During the three year period of this database
there was only one infant who had only a
weakly positive DCT and required an XT.

We were interested to read Dr 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 prod-
uct. 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
infants 4 and is currently being used in the
INTS Trial. 4 As with any drug, the additional
blood product we will need to remain vigilant for the occur-
rence of any adverse events.

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hyperbilirubinemia in rhesus hemolytic

Role of serum peak levels of
vancomycin in neonatal
intensive care units

We would like to comment on the article by Tan et al. 5 The purpose of measuring serum
levels of a drug is either to monitor the toxicity
of the drug or the therapeutic concentration
for a particular condition. Emergence of infections with β-lactam-resistant Staphylo-
coccus epidermidis, Staphylococcus aureus, and Ente-
roccus 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, including
ototoxicity and nephrotoxicity, were prob-
able due impurities in the formulation. 6
Now that a more purified form is available, these
adverse reactions are uncommon. However,
concomitant administration with aminogly-
cosides or other nephrotoxic drugs 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-
centration only 7 as this study is clearly
documented, but others have suggested not
measuring any concentrations in the majority
of children with normal renal function. 7
However, in critically ill premature neonates
with poor glomerular filtration rate, prematu-
rity, 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. 8 In this study, the authors
did not mention the concomitant use of
aminoglycoside.

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regimen for vancomycin not needing serum

www.archdischild.com

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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 DNB; half a capsule a day, equivalent to 2.5 × 10^9 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, which was resistant 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 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 34cm by 37cm 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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We wish to apologise for an error that occurred in a letter by Daniels et al (Arch Dis Child Fetal Neonatal Ed 2003;88(F):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.”