Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn

R Gottstein, R W I Cooke

Objective: To assess the effectiveness of high dose intravenous immunoglobulin (HDIVIG) in reducing the need for exchange transfusion in neonates with proven haemolytic disease due to Rh and/or ABO incompatibility. To assess the effectiveness of HDIVIG in reducing the duration of phototherapy and hospital stay.

Design: Systematic review of randomised and quasi-randomised controlled trials comparing HDIVIG and phototherapy with phototherapy alone in neonates with Rh and/or ABO incompatibility.

Results: Significantly fewer infants required exchange transfusion in the HDIVIG group (relative risk (RR) 0.28 (95% confidence interval (CI) 0.17 to 0.47); number needed to treat 2.7 (95% CI 2.0 to 3.8)). Also hospital stay and duration of phototherapy were significantly reduced.

Conclusion: HDIVIG is an effective treatment.

In this systematic review, we evaluate the role of postnatal administration of HDIVIG to neonates with HDN.

METHODS

Criteria for considering studies

We identified randomised and quasi-randomised controlled trials of infants with proven Rh and/or ABO HDN reporting on at least one of the following outcomes: number of exchange transfusions, length of phototherapy, or length of hospital stay. The interventions under investigation were HDIVIG with phototherapy or phototherapy alone. Thus all infants received phototherapy and the only variable was the postnatal administration of HDIVIG. There were no birth weight or gestational age limits, and no limitation on severity of haemolytic disease or whether the infants or their mothers received antenatal treatment. Trials were not limited in terms of dose or duration of HDIVIG infusion.

Literature search

The literature search was performed in November 2000 using Medline (1986–2000), Embase (1984–2000), and Cochrane Library Controlled Trials Registers using the following subject and text word terms: “neonate(s), newborn(s), or infant(s)”; “rhesus incompatibility, rhesus isoimmunization, rhesus alloimmunisation, rhesus alloimmunization, ABO incompatibility, ABO isoimmunization, ABO isoimmunization, h(a)emolytic disease, h(a)emolytic jaundice or erythroblasto-
sis (f)etalis”; and “immunoglobulin, immune globulin, or gammaglobulin”. A manual search of the Journal of Pediatrics (1985–2000), Pediatrics (1990–2000), and Archives of Disease in Childhood (1990–2000) was conducted and included abstracts submitted to scientific meetings. Additional citations were sought using references in articles retrieved from the searches. Unpublished and further published trials were sought from experts in the field. Searches were not limited by language.

Abbreviations: IVIG, intravenous immunoglobulin; HDIVIG, high dose IVIG; HDN, haemolytic disease of the newborn; RR, relative risk; RD, risk difference; WMD, weighted mean difference; CI, confidence interval; NNT, number needed to treat.
Table 1 Characteristics of studies included

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Gestation</th>
<th>Birth weight (g)</th>
<th>No of infants in study</th>
<th>IVIG dose</th>
<th>Exchange transfusion criteria</th>
<th>Outcomes reported</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpay et al</td>
<td>Single centre, random number, sealed envelopes</td>
<td>ABO and/or Rh HDN, DCT +ve, Retics</td>
<td>36.1(2.3)</td>
<td>36.1(1.7)</td>
<td>3119* (546)</td>
<td>0.5 g/kg</td>
<td>SBR &gt;340 µmol/l and increasing by &gt;17 µmol/l/hour</td>
<td>Exchange transfusion, postnatal age, birth weight and SBR, as defined in their paper</td>
<td>1</td>
</tr>
<tr>
<td>Daggoğlu et al</td>
<td>Single centre, Rh HDN, DCT +ve, Rh ~ve Mum</td>
<td>nk</td>
<td>31.1(1.7)</td>
<td>31.1(1.7)</td>
<td>2851 (469)</td>
<td>0.5 g/kg</td>
<td>SBR &gt;340 µmol/l and increasing by &gt;17 µmol/l/hour</td>
<td>Exchange transfusion, late anaemia</td>
<td>1</td>
</tr>
<tr>
<td>Rübo et al</td>
<td>Multicentre, Rh HDN, DCT +ve, Rh ~ve Mum</td>
<td>nk</td>
<td>31.1(2.5)</td>
<td>31.1(2.5)</td>
<td>2803 (573)</td>
<td>0.5 g/kg</td>
<td>SBR &gt;340 µmol/l and increasing by &gt;17 µmol/l/hour</td>
<td>Exchange transfusion, late anaemia</td>
<td>1</td>
</tr>
<tr>
<td>Vato et al</td>
<td>Single centre, Rh HDN, DCT +ve, RH +ve infant</td>
<td>nk</td>
<td>37.3(3)</td>
<td>37.5(2.5)</td>
<td>2866 (579)</td>
<td>0.5 g/kg</td>
<td>SBR &gt;340 µmol/l and increasing by &gt;17 µmol/l/hour</td>
<td>Exchange transfusion, late anaemia</td>
<td>1</td>
</tr>
</tbody>
</table>

Gestation and birth weight are given as means (SD).

*Information given in Rübo and Wahn.

IVIG, Intravenous immunoglobulin group; C, control group; Rh, rhesus; HDN, haemolytic disease of the newborn; DCT, direct Coomb’s test; Retics, reticulocyte count; SBR, serum bilirubin; nk, not known.

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**Outcomes measured**

Three studies (n = 139) reported on the number of exchange transfusions given.* The fourth study reported on the number of exchange and red cell transfusions together, and the results showed a small difference in the number of transfusions between the two groups in that study. The authors concluded that IVIG was associated with a reduction in the number of exchange transfusions, and that the difference was statistically significant.

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**Results**

From the literature search, six randomised controlled trials were identified as meeting the criteria for inclusion in the review. One publication describes a previously reported study. Two were excluded on the basis of protocol violations, the results of the remaining four trials were included in the analysis.

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*Information given in Rübo and Wahn.

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The methodological quality was assessed using Jadad criteria. Five studies (n = 139) were included in this meta-analysis, with the remaining five studies excluded due to methodological limitations.

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The statistical package (RevMan version 4.1) was used to perform the meta-analysis. The data were analysed on an intention to treat basis, and the results were presented as risk ratios (RR) and risk differences (RD) using the fixed effects model. The data were not analysed on an intention to treat basis, and the results were presented as risk ratios (RR) and risk differences (RD) using the fixed effects model.
For neonates with Rh haemolytic disease only (n = 73), there is a further reduction in need for exchange transfusion (RR 0.21 (95% CI 0.10 to 0.45), RD −0.59 (95% CI −0.77 to −0.40), NNT 1.7 (95% CI 1.3 to 2.5)) (fig 2). There is also a significant reduction in the number of neonates requiring multiple exchange transfusions with HDIVIG treatment (RR 0.22 (95% CI 0.08 to 0.61), RD −0.15 (95% CI −0.24 to −0.06)) (fig 3).

There is a significant reduction in the length of hospital stay with the use of HDIVIG treatment in addition to phototherapy (WMD −1.06 (95% CI −1.65 to −0.46)) (fig 4). However, there is significant heterogeneity between the studies. Two studies19 19 reported on this outcome (n = 153). Voto et al19 found a considerably longer hospital stay. There is a significant reduction in the duration of phototherapy required with HDIVIG treatment in addition to phototherapy (WMD −0.87 (95% CI −1.37 to −0.37)) (fig 5). Two studies15 19 reported on this outcome; there was no difference in the two groups. Rübo et al17 reported that there was no difference

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (95% CI fixed)</th>
<th>Weight (%)</th>
<th>RR (95% CI fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpay et al15</td>
<td>3/58</td>
<td>7/58</td>
<td>38.1 (0.43 (0.12 to 1.58)</td>
<td>98.5</td>
<td>−0.98 (−1.58 to −0.38)</td>
</tr>
<tr>
<td>Dagoglu et al16</td>
<td>0/22</td>
<td>5/19</td>
<td>32.0 (0.08 (0.00 to 1.34)</td>
<td>1.5</td>
<td>−6.00 (−10.81 to −1.19)</td>
</tr>
<tr>
<td>Rübo et al17</td>
<td>0/16</td>
<td>5/16</td>
<td>29.9 (0.09 (0.01 to 1.52)</td>
<td>100.0</td>
<td>−1.06 (−1.65 to −0.46)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3/96</td>
<td>17/93</td>
<td>100.0</td>
<td>0.22 (0.08 to 0.61)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

Figure 3 Number of infants requiring multiple exchange transfusions when comparing high dose intravenous immunoglobulin with phototherapy alone.
between the two groups with respect to duration of phototherapy, although the data were not published.

There is an increase in the number of red cell transfusions required for late anaemia in those infants who received HDI-VIG. This just reached significance with very wide confidence intervals (RR 8.0 (95% CI 1.03 to 62.2), RD 0.07 (95% CI 0.01 to 0.14)) (fig 6). Three studies (n = 189) reported on this outcome.15–17 The criteria used in determining when these infants should be transfused were not always apparent.

Reports of adverse events

Three studies report that the infants were monitored closely for possible side effects of administration of HDIVIG. They observed infants for possible febrile, allergic, haemolytic, and volume overloading side effects of HDIVIG by observation of changes in body temperature, respiratory rate and pattern, heart rate, and blood pressure. None experienced any adverse events with the use of HDIVIG. Problems were, however, seen in infants of the control group who required exchange transfusions. Rübo et al17 report a case with inspissated bile syndrome and another with bacterial sepsis. A causal link was not established. Alpay et al15 report two cases in the control group who developed hypoglycaemia and hypocalcaemia after exchange transfusions.

DISCUSSION

Since the advent and widespread use of anti-D immunoglobulin prophylaxis in preventing sensitisation of Rh negative mothers, the incidence of Rh haemolytic disease of the newborn has fallen dramatically, although it still exists. In fact, anti-D remains the most common cause of morbidity and mortality from haemolytic disease, although its prevalence in relation to other red cell antibodies has appreciably declined.21 During a 12 month study of seven maternity units in Mersey and North Wales in 1993/1994, clinically important red cell antibodies were detected in 1% of the study population.22 The morbidity and mortality associated with exchange transfusions are not insignificant.21 As the incidence of HDN has decreased in recent years, paediatricians are less experienced at performing exchange transfusions, and thus one might postulate that the morbidity associated with this procedure is likely to increase. To reduce the risks of exchange transfusions at the hands of inexperienced staff, the options for less invasive effective treatments such as HDIVIG should be explored.

The “number needed to treat” in order to prevent one exchange transfusion is very low at 2.7 (95% CI 2.0 to 3.8). However, in these studies a large proportion of babies with Rh or ABO incompatibility in the control group required exchange transfusion despite phototherapy. The exchange transfusion rate in the controls is higher than may be expected in the United Kingdom. It is unclear why this is so. The exchange transfusion criteria used in the trials are fairly conventional. The difference may arise for a variety of reasons. Changes have occurred in the natural history of Rh disease with the use of anti-D and also in reproductive practice in Northern Europe. We can postulate that (a) there are differences in antenatal antibody screening, (b) direct Coomb’s tests may only be performed on infants with very aggressive haemolysis, (c) phototherapy may have been inadequate, or (d) there are other differences between the practices or populations in the United Kingdom and Turkey, Argentina, and Germany. Therefore it can be argued that the NNT in the United Kingdom would be higher than that reported in this systematic review. Nevertheless, HDIVIG is an effective treatment in reducing the exchange transfusion rate in neonates with HDN. Even in countries such as the United Kingdom where exchange transfusions are rarely performed in this clinical setting, the NNT would remain low if this treatment were reserved for infants with severe haemolysis, in whom the potential need for exchange transfusion is highest.

This review has shown a reduction in the duration of phototherapy and hospital stay when HDIVIG is used in addition to phototherapy for HDN. The financial saving from the shortened inpatient stay and duration of phototherapy offsets the cost of IVIG.

All the studies included showed a beneficial effect, despite the variation in IVIG doses. It appears that a single dose of 0.5 g/kg on day 1 is as effective as any other treatment regimen. Some authors have implied that the key to successful
treatment is the early administration of the immunoglobulin, as soon as the diagnosis of haemolytic anaemia is made. When HDN is treated with HDIVIG in addition to phototherapy, there is a reduction in the degree of haemolysis and therefore the need for exchange transfusion. As the antibody has not been “washed out” (as would be the case during an exchange transfusion), there may be late haemolysis and anaemia. When the effect of the HDIVIG has worn off, the Fe sites on the surface of the reticuloendothelial cells become free to bind antibody sensitised neonatal erythrocytes, thus causing haemolysis. This is postulated to be the reason for the excess late red cell transfusions required in the HDIVIG treated group. The incidence of late anaemia may in fact be similar to that occurring in infants who had moderate haemolysis but did not require exchange transfusions.

At present, IVIG is licensed for use in primary immunodeficiencies and secondary immunodeficiencies such as chronic lymphocytic leukaemia, idiopathic thrombocytopenic purpura, Kawasaki disease, Guillain Barré syndrome, and paediatric AIDS. It is also used for intractable epilepsy and juvenile dermatomyositis. Although considered to be a relatively safe product, it is not without risk of adverse reactions. The identification of more than 100 patients with hepatitis C apparently acquired from a single immunoglobulin product is a reminder that IVIG is a biological product derived from pooled human plasma. To reduce the risk of transmission of infective agents, donors and donations are selected and plasma pools are tested and undergo a viral partitioning and inactivation process. However, the small risk of potential transfusion transmitted diseases will remain.

Other adverse effects reported from the use of IVIG include headache, meniscus, fever, nausea, low back pain, transient hypotension, and, rarely, a mild, usually clinically irrelevant, haemolytic anaemia. These adverse effects are usually mild and transient. Serious side effects are very rare and include hypersensitivity and anaphylactic reactions, which can occur in patients with IgA deficiency or hypogammaglobulinemia as a result of the presence of IgA antibodies in the patient’s serum.

Implications for future research
The evidence presented in this systematic review of the available randomised controlled trials of HDIVIG administered in the postnatal period in HDN shows a significant effect for HDIVIG. Thus, it may be considered unethical to delay wider use of HDIVIG while carrying out further research. The optimum treatment dose and frequency is as yet uncertain and this may be an area for further research. Multiple doses of IVIG may reduce the late anaemia and therefore reduce the need for red cell transfusions. In the study investigating the role of repeated doses of HDIVIG, there appears to be a reduction in the need for exchange transfusion in the group receiving a second dose of IVIG 48 hours after the first. However, the numbers are small (25 in each study arm), and flaws occurred in the method of randomisation.

References