Effect of fresh frozen plasma and gammaglobulin on humoral immunity in neonatal sepsis

B A Acunas, M Peakman, G Liossis, E T Davies, B Bakoleas, C Costalos, H R Gamsu, D Vergani

Abstract
Fresh frozen plasma and intravenous immunoglobulin are used as prophylaxis against, and for the treatment of, neonatal infection. It is assumed that any beneficial effect is mediated through the humoral immune factors contained in each preparation. The effect of fresh frozen plasma and intravenous immunoglobulin on humoral immune markers (immunoglobulins and IgG subclasses, complement components and activation products, and C reactive protein) was investigated over a 24 hour period after their randomised administration to 67 infants with suspected infection. Thirty infants without suspicion of infection were studied as controls. Compared with control infants, infants with suspected infection had increased concentrations of C reactive protein, reduced concentrations of fibronectin, and increased concentrations of the complement activation marker C3d, but similar concentrations of IgG, IgG subclasses, IgA, and IgM. After intravenous immunoglobulin treatment (500 mg/kg) concentrations of total IgG and all IgG subclasses increased, as did IgA and complement component C4. Concentrations of C reactive protein decreased after intravenous immunoglobulin treatment and were significantly lower than baseline after 24 hours. In contrast, no change in IgG or IgG subclass concentrations occurred after fresh frozen plasma administration. At 24 hours after fresh frozen plasma administration, concentrations of IgA, IgM, and C4 were significantly higher than baseline and serum IgA was significantly higher than in infants tested 24 hours after intravenous immunoglobulin treatment. These results confirm the rational basis for intravenous immunoglobulin treatment but question the value of fresh frozen plasma, particularly in the light of its attendant problems as an untreated blood product.

Numerous humoral deficiencies in term and premature neonates seem to be crucial contributory factors to the increased susceptibility to infection seen at this age. These include low concentrations of IgG in preterm infants due to lack of placental transfer, deficiency of IgG subclasses, decreased concentrations of circulating complement factors, and decreased concentrations of circulating fibronectin. In the last decade various studies have been undertaken in an attempt to show an enhancement of the neonatal host defence mechanism by the use of granulocyte transfusions, therapeutic exchange transfusions, and intravenous immunoglobulins. Among these immunotherapeutic strategies, intravenous immunoglobulin has been widely used prophylactically, especially in very low birthweight neonates given single or repeated doses and as an adjunctive treatment in patients with sepsis; this treatment has been shown to result in improved survival. In addition, fresh frozen plasma is widely used as a putative source of immunoglobulins and complement factors to provide an adjunctive treatment in the management of neonatal sepsis. There have been no studies to determine whether fresh frozen plasma has any effect on components of the neonatal immune system, however. The aim of this study was to determine the effect of fresh frozen plasma on the major components of neonatal humoral immunity such as immunoglobulins, complement factors, and fibronectin, and to compare these with the effect if intravenous immunoglobulin on the same factors.

Subjects and methods

Between February 1991 and March 1993 two neonatal centres participated in this study; the neonatal unit of the general hospital in Piraeus, Greece and the Children Nationwide Regional Neonatal Centre of King’s College Hospital, London. Newborn infants with ‘possible’ or ‘probable’ infection who fulfilled the clinical/laboratory criteria for these diagnoses as described previously were enrolled. Neonates with severe congenital malformations, viral embryopathy, and those in whom death was considered inevitable were excluded. Previous treatment of the mother with antibiotics did not exclude entry of infants into the study. Infants were enrolled into the study when they had their first suspected episode of infection. After written informed consent was obtained from their parents, the infants were randomly assigned to receive either fresh frozen plasma or intravenous immunoglobulin using a sealed envelope.
method within one to six hours of the development of clinical signs of infection. In an attempt to provide an equal distribution of premature (<37 weeks’ gestation) and term infants (≥37 weeks’ gestation), two sets of sealed envelopes were used (one for preterm, one for term infants). A group of infants without suspicion of infection and matched for age, birth weight, and gestational age was concurrently enrolled as the control group. It was considered unethical to include a placebo group when neonatal infection was suspected. The study was approved by the research ethics committee of Camberwell Health Authority, London, and the ethical committee of Piraeus General Hospital.

Fresh frozen plasma compatible with the blood group of the infant to be transfused was supplied from the appropriate blood bank and had been screened serologically for hepatitis B, cytomegalovirus, and HIV. The intravenous immunoglobulin used in this study (Sandoglobulin, from Sandoz Pharmaceuticals manufactured by the Central Laboratory, Swiss Red Cross, Berne, Switzerland) was lyophilised human normal immunoglobulin (3 g/100 ml vial with 5% sucrose). Three lots of Sandoglobulin (lot numbers 032623120, 23652370, 23652000) were used in the study. Fresh frozen plasma (15 ml/kg body weight) or Sandoglobulin (500 mg/kg body weight) was infused through a peripheral intravenous catheter, avoiding mixing with other solutions or drugs. The infusion rate was 0-02 ml/kg/minute initially and thereafter this was increased every 15 minutes to a maximum infusion rate of 0-15 ml/kg/minute. Before the infusion of fresh frozen plasma patients with suspected necrotising enterocolitis were screened with a specific agglutination test using peanut lectin derived from Arachis hypogea to detect T cell activation. None of the infants studied was positive on testing for T antigen activation. During the infusion, vital signs (heart rate, respiratory rate, body temperature, and blood pressure) were closely monitored as well as signs of adverse reactions such as flushing, fever, emesis, restlessness, and irritability.

All infants with suspected infection (possible or probable) were screened microbiologically using microscopy and culture examination of swabs taken from the ear, nose, endotracheal tube, and umbilicus, and similarly cultures were made of body fluids (blood, cerebrospinal fluid, urine, and gastric aspirate). Blood was also taken for haemoglobin concentration, leucocyte and platelet counts, and leucocyte differential. Infection was considered proved if blood or cerebrospinal fluid cultures were positive or cultures from urine or from more than two swab sites were 3+ positive (defined as heavy confluent growth after overnight culture) with a pure growth of a single organism.

**Table 1.** Demographic data for infants treated with fresh frozen plasma (FFP) and intravenous immunoglobulin (IVG), and infants in the control group

<table>
<thead>
<tr>
<th></th>
<th>FFP group (n=34)</th>
<th>IVG group (n=33)</th>
<th>Control group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SEM) gestational age (weeks)</td>
<td>34 (4-82)</td>
<td>35-21 (4-41)</td>
<td>35-63 (3-19)</td>
</tr>
<tr>
<td>Mean (SEM) birth weight (g)</td>
<td>1990 (880)*</td>
<td>2410 (880)</td>
<td>2050 (880)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>61</td>
<td>75</td>
<td>53</td>
</tr>
<tr>
<td>Mean (SEM) postnatal age (days)</td>
<td>9 (10-3)</td>
<td>7-4 (7-7)</td>
<td>10-2 (10-6)</td>
</tr>
<tr>
<td>Premature (%)</td>
<td>70</td>
<td>51</td>
<td>60</td>
</tr>
<tr>
<td>Possible infection (%)</td>
<td>41</td>
<td>45</td>
<td>56</td>
</tr>
<tr>
<td>Probable infection (%)</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Proven infection (%)</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Mean (SEM) leucocyte count (×10⁹/l)</td>
<td>3-36 (7-20)</td>
<td>3-46 (7-78)</td>
<td>11-13 (5-16)</td>
</tr>
<tr>
<td>Mean (SEM) neutrophil count (×10⁷/l)</td>
<td>7-47 (4-69)</td>
<td>8-31 (5-47)</td>
<td>8-64 (5-72)</td>
</tr>
<tr>
<td>Mean (SEM) platelet count (×10⁹/l)</td>
<td>345 (443)</td>
<td>278 (142)</td>
<td>318 (146)</td>
</tr>
</tbody>
</table>

No of deaths | 3 | 3 | None |

*p<0.05 compared with IVG group.

**DEMOGRAPHIC DATA**

Seventy seven infants with suspected infection were initially randomised into the study. Ten of these were excluded because of previous treatment with fresh frozen plasma or because they received fresh frozen plasma during the sampling period after having been transfused with intravenous immunoglobulin. Thirty infants without suspicion of infection were enrolled as the control group. Table 1 gives the demographic and laboratory/clinical data on these infants and on the 67 with suspected infection. There was no significant difference in the fresh frozen plasma, intravenous immunoglobulin, and control groups with respect to gestational age, postnatal age, and sex (table 1). There was, however, a small difference in birthweight between the fresh frozen plasma and intravenous immunoglobulin groups (p=0.04). The treated groups had a similar distribution of possible or probable infection. Twenty five patients (15 (44%) of the 34 fresh frozen plasma recipients and 10 (30%) of the 33 intravenous immunoglobulin recipients) had proven infection. Nine infants were infected with Escherichia coli (five fresh frozen plasma, four intravenous immunoglobulin), five with Staphylococcus epidermidis (three fresh frozen plasma, two intravenous immunoglobulin), four with Staphylococcus aureus (four fresh frozen plasma, one intravenous immunoglobulin), three with Lancefield group B streptococcus (two fresh frozen plasma, one intravenous immunoglobulin), two with enterobacter (one fresh frozen plasma, one intravenous immunoglobulin), one with citrobacter (fresh frozen plasma), and one with Klebsiella pneumoniae (intravenous immunoglobulin). Four of these infants were diagnosed as having proved infection on the basis of 3+ positive superficial swabs. One receiving fresh frozen plasma had a pure growth of Lancefield group B streptococcus from the nose, ear, umbilicus, gastric aspirate samples, and a maternal high vaginal swab was 3+ positive for the same organism. In the other three infants (all receiving intravenous immunoglobulin), 3+ positive cultures with pure growth of E coli, citrobacter, and Lancefield group B streptococcus were obtained from the nose, ear, umbilicus, and gastric aspirate samples. In two of these infants cord blood samples were also culture positive, and in the other infant endotracheal tube secretions were culture positive.
Table 2 Effect of fresh frozen plasma (FFP) and intravenous immunoglobulin (IVIG) infusions on plasma concentrations of complement factors, fibropectin, and C reactive protein. Values are median (range).

<table>
<thead>
<tr>
<th>Group</th>
<th>C3 (AU/l)</th>
<th>C5 (g/l)</th>
<th>C4 (g/l)</th>
<th>Fibropectin (mg/l)</th>
<th>C reactive protein (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>615 (40-4100)</td>
<td>0.64 (0.31-1.25)</td>
<td>0.16 (0.04-0.50)</td>
<td>156 (68-447)</td>
<td>11.4 (0.6-280)</td>
</tr>
<tr>
<td>After 12 hours</td>
<td>555 (40-7040)</td>
<td>0.68 (0.11-1.16)</td>
<td>0.18 (0.03-0.35)</td>
<td>135 (75-542)</td>
<td>17.1 (0.6-246)</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>712 (40-5080)</td>
<td>0.73 (0.33-1.28)</td>
<td>0.26 (0.07-1.0)</td>
<td>ND</td>
<td>19.1 (0.6-249)</td>
</tr>
<tr>
<td>IVIG group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>625 (44-8000)*</td>
<td>0.76 (0.35-1.23)</td>
<td>0.17 (0.07-0.39)</td>
<td>148 (92-273)</td>
<td>24.1 (0.6-253)</td>
</tr>
<tr>
<td>After 12 hours</td>
<td>357 (680-5200)</td>
<td>0.72 (0.35-1.32)</td>
<td>0.17 (0.06-0.38)</td>
<td>201 (20-497)</td>
<td>9.0 (0.6-1287)</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>532 (78-6640)</td>
<td>0.78 (0.40-1.31)</td>
<td>0.19 (0.09-0.90)</td>
<td>ND</td>
<td>7.2 (0.6-88.6)</td>
</tr>
<tr>
<td>Normal infants</td>
<td>291 (10-2220)</td>
<td>0.60 (0.23-1.08)</td>
<td>0.18 (0.05-0.42)</td>
<td>218 (114-148)</td>
<td>0.7 (0.60-10-2)</td>
</tr>
</tbody>
</table>

ND = Not done; AU/l = arbitrary units/l.
*p<0.01 v normal infants; tP<0.0005 v normal infants; §P<0.0001 v normal infants; ¶P<0.05 v baseline; †P<0.01 v baseline.

No differences were observed between fresh frozen plasma and intravenous immunoglobulin recipients with respect to initial leucocyte, neutrophil, and platelet counts (table 1). There were three deaths in the fresh frozen plasma treated group: one from group B streptococcal septicaemia, severe respiratory distress syndrome, and grade IV intraventricular haemorrhage two days after enrolment into the study; one from Staphylococcus aureus septicaemia, also two days after enrolment; and the third died 30 days after enrolment due to severe bronchopulmonary dysplasia. Similarly, there were three deaths in the intravenous immunoglobulin treated group: one from enterobacter septicaemia on day 9; one from ventricular septal defect and congestive heart failure on day 10; and one from candida septicaemia after two months. No adverse effects were observed with either treatment during or after infusion.

MEASUREMENT OF COMPONENTS OF HUMORAL IMMUNITY
Specimens of 1 ml blood in 10 mmol EDTA and samples from the fresh frozen plasma to be transfused into the infants were collected immediately before the administration of either fresh frozen plasma or intravenous immunoglobulin and from the control group from whom blood was being taken for management purposes. A 1 ml blood sample from the treated infants was also drawn into EDTA at 12 and 24 hours after treatment. Plasma was separated by centrifugation and stored at -70°C. Immunoglobulin classes A and M, intact complement components C3 and C4, C reactive protein, and fibropectin were measured by nephelometry according to the manufacturer's instructions (Behring Diagnostics, Hounslow, Middlesex). Total IgG and IgG subclasses were measured by nephelometry using kits supplied by The Binding Site, Birmingham.

All assays were carried out by investigators who were unaware of the clinical details. Insufficient plasma was available for all tests to be performed at each time point therefore IgG subclasses, total IgG, and fibropectin were measured only on the first (preinfusion) and second (at 12 hours after infusion) samples.

Concentrations of the complement activation product C3d were determined by an enzyme linked immunosorbent assay (ELISA) using a commercial source of unlabelled and peroxidase labelled antibody to C3d (Dako, High Wycombe) as previously described.18

STATISTICAL ANALYSIS
Comparability of the demographic data of the fresh frozen plasma, intravenous immunoglobulin treated, and control groups on enrolment was assessed using Student's t test. The distribution of concentrations of immunoglobulins, C3, C4, C reactive protein, fibropectin, and C3d did not fit the hypothesis of normality as assessed by the Kolmogorov-Smirnov goodness of fit test. Values were therefore expressed as medians (range) and comparisons between groups were performed using the Mann-Whitney U test. Changes in analytes after treatment at 12 and 24 hours were compared using the Wilcoxon signed rank test for matched pairs. All analyses were performed using the Statistical Package for the Social Sciences (SPSS-X) of the University of London Computer Centre Amdahl 5980/300. A two tailed p value less then 0.05 was considered to indicate a significant difference.

Results
CONCENTRATION OF MARKERS OF HUMORAL IMMUNITY AT ENTRY
Samples from the fresh frozen plasma and intravenous immunoglobulin treatment groups taken at the time of the study showed that concentrations of C reactive protein were significantly higher (p<0.0001 for the two groups) and concentrations of fibropectin significantly lower (p<0.005) than in the control group (table 2). In the intravenous immunoglobulin treated group, concentrations of C3 and C3d were significantly increased compared with control subjects (p<0.005 and p<0.01). Concentrations of IgG and its subclasses, IgA, IgM, and IgC were similar in the treated and control groups. Levels of all parameters were similar in the two treatment groups.

CHANGES IN MARKERS OF HUMORAL IMMUNITY AFTER FRESH FROZEN PLASMA TREATMENT
A significant increase in concentrations of IgM and IgA was seen 12 hours after fresh frozen plasma treatment (p<0.005 and p<0.01)
Effect of fresh frozen plasma and gammaglobulin on humoral immunity in neonatal sepsis

Table 3: Effect of fresh frozen plasma (FFP) and intravenous immunoglobulin (IVIG) infusions on plasma concentrations of immunoglobulins. Values are median (range)

<table>
<thead>
<tr>
<th>Group</th>
<th>IgG1 (g/l)</th>
<th>IgG2 (g/l)</th>
<th>IgG3 (g/l)</th>
<th>IgG4 (g/l)</th>
<th>Total IgG (g/l)</th>
<th>IgM (g/l)</th>
<th>IgA (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP group</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.85 (1.58-8.46)</td>
<td>1.31 (0.54-4.37)</td>
<td>0.35 (0.18-0.75)</td>
<td>0.23 (0.08-0.91)</td>
<td>6.13 (2.94-11.40)</td>
<td>0.14 (0.09-0.96)</td>
<td>0.07 (0.07-1.52)</td>
</tr>
<tr>
<td>After 12 hours</td>
<td>3.73 (1.91-11.10)**</td>
<td>1.32 (0.70-2.81)**</td>
<td>0.35 (0.08-0.72)</td>
<td>0.22 (0.09-0.94)†</td>
<td>6.38 (3.17-11.40)**</td>
<td>0.22 (0.09-0.61)†</td>
<td>0.17 (0.07-0.60)‡</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>IVIG group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.04 (2.09-9.34)</td>
<td>1.23 (0.64-3.45)</td>
<td>0.32 (0.12-0.82)</td>
<td>0.18 (0.07-0.81)</td>
<td>6.04 (2.66-13.70)</td>
<td>0.16 (0.09-1.12)</td>
<td>0.07 (0.07-0.55)</td>
</tr>
<tr>
<td>After 12 hours</td>
<td>6.63 (3.81-11.10)$</td>
<td>2.55 (1.83-14.05)</td>
<td>0.52 (0.21-2.12)</td>
<td>0.32 (0.14-0.33) $</td>
<td>10.80 (5.77-16.80)</td>
<td>0.17 (0.09-1.14)</td>
<td>0.08 (0.07-0.51)†</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Normal infants</td>
<td>3.82 (1.59-8.11)</td>
<td>1.12 (0.40-2.79)</td>
<td>0.55 (0.12-0.92)</td>
<td>0.21 (0.08-0.57)</td>
<td>5.30 (2.25-10.90)</td>
<td>0.22 (0.09-0.53)</td>
<td>0.07 (0.07-0.23)</td>
</tr>
</tbody>
</table>

ND=not done.
*p<0.05 v baseline; $p<0.01 v baseline; $p<0.005 v baseline; $p<0.001 v baseline; †p<0.05 v IVIG group; ‡p<0.005 v IVIG group; **p<0.0001 v IVIG group; ††p<0.05 v FFP group.

Compared with baseline (table 3). At 24 hours concentrations of IgM and IgA remained increased compared with baseline (p<0.001 for the two groups) and C4 was significantly higher than the pretreatment concentration (p<0.05). There was no change in the other markers of humoral immunity after fresh frozen plasma treatment.

Changes in markers of humoral immunity after intravenous immunoglobulin treatment

A significant increase in total IgG and in all four IgG subclasses (p<0.0001 for all) and also in IgA (p<0.005) was seen 12 hours after the start of intravenous immunoglobulin treatment compared with baseline (table 3). Concentrations of total IgG and IgG subclasses were not measured at 24 hours but concentrations of IgA remained significantly increased compared with baseline at this time (p<0.05). Concentrations of C4 were increased at 24 hours compared with baseline (p<0.05). Concentrations of C reactive protein did not change in the first 12 hours after treatment, but decreased significantly in the second 12 hours (p<0.05). At 24 hours C reactive protein concentrations were significantly lower than before treatment started (p<0.01). There was no change in the other markers of humoral immunity after intravenous immunoglobulin.

Comparison of fresh frozen plasma and intravenous immunoglobulin treated groups

At 12 hours after the start of treatment concentrations of total IgG and IgG subclasses were significantly higher in the intravenous immunoglobulin than in the fresh frozen plasma treated group (p<0.0001 for total IgG, IgG1, and IgG2; p<0.001 for IgG3; and p<0.05 for IgG4) (table 3). At 24 hours after the start of treatment, concentrations of IgA were significantly higher in the fresh frozen plasma than in the intravenous immunoglobulin treated group (p<0.05).

Changes in markers of humoral immunity in preterm infants

To examine whether changes in humoral markers after treatment with fresh frozen plasma or intravenous immunoglobulin were different in more than in less mature infants, treatment groups were divided according to gestational age (<35 v ≥35 weeks). Overall, infants <35 weeks' gestation and those ≥35 weeks have similar results to those of the group as a whole. There were some small differences, however. In the fresh frozen plasma treated group, C4 concentrations were higher at 24 hours than at baseline (p<0.05), but only in infants <35 weeks' gestation. In addition, though concentrations of IgA did not change within the first 12 hours after fresh frozen plasma treatment in infants <35 weeks' gestation, concentrations at 24 hours were significantly higher than at baseline (p<0.05). In contrast, in infants ≥35 weeks' gestation, IgA concentrations increased at 12 hours and remained increased compared with baseline (p<0.005 and p<0.05). In the intravenous immunoglobulin treated group changes seen in infants <35 weeks' and ≥35 weeks' gestation were identical to each other and to those seen in the undivided group.

Levels of humoral markers present in fresh frozen plasma and intravenous immunoglobulin

Table 4 gives the concentrations of IgM, IgA, IgG subclasses, C reactive protein, C3, C4, C3d, and fibronectin in fresh frozen plasma and intravenous immunoglobulin.

Discussion

Supplementation of the circulating proteins of neonates prophylactically or after the diagnosis of sepsis is associated with an increase in C reactive protein and total IgA and G subclasses. The significant increase in total IgG and C reactive protein could be of potential significance in the discussion of the pathogenesis of neonatal sepsis.
of suspected infection is carried out with the aim of enhancing humoral immunity. There are two main sources of humoral immune components in current use: fresh frozen plasma and immunoglobulin. Few studies, however, have addressed the question of the efficacy of intravenous immunoglobulin in providing humoral immune components, and none the role of fresh frozen plasma. In this study we showed that intravenous immunoglobulin treatment increases circulating concentrations of all IgG subclasses, as well as increasing IgA and complement C4 concentrations. C reactive protein, a marker of infection in neonates, decreased in the immunoglobulin treated group. In contrast, the administration of fresh frozen plasma had no effect on IgG antibody levels, but resulted in increased concentrations of circulating IgA, IgM, and C4. These results confirm the rational basis for intravenous immunoglobulin treatment but question the value of fresh frozen plasma, particularly in light of its attendant problems as an untreated blood product.

Efficient phagocytosis and killing of pathogenic organisms by neutrophils only occurs after antibody, complement, and fibronectin proteins are deposited on the surface of bacteria. 

In this respect, neonatal host defences provide inadequate host protection because concentrations of these opsonins are low. Fresh frozen plasma contains the labile as well as the stable components of the coagulation, fibrinolytic, and complement systems, and humoral components of immunity such as immunoglobulins and fibronectin. Fresh frozen plasma should therefore be effective in supplementing humoral mechanisms of neonatal host defence. This study did not show a beneficial effect of fresh frozen plasma on humoral immunity in neonates, however, other than increasing the concentrations of IgA, IgM, and C4. The significance of increasing circulating IgA is questionable as IgA functions predominantly as secreted antibody at mucosal surfaces. Infusion of intravenous immunoglobulin was not a cause of a significant increase in total IgG and all its subclasses. This confirms a previous report by Christensen et al, 

which also did not show any effect of intravenous immunoglobulin on C3 24 hours after infusion.

Baseline plasma concentrations of C3d and C reactive protein were significantly higher in patients with suspected infection than in the control group in our study, confirming our previous report. C reactive protein is an opsonin and acts as an acute phase reactant, concentrations increasing during inflammatory episodes. C3d, on the other hand, is a breakdown product of C3 and is presumably generated in these infants as a result of complement activation occurring on the bacterial surface. C reactive protein concentrations decreased after intravenous immunoglobulin, possibly as a result of confinement of the bacterial infection and limitation of the release of cytokines which provoke the release of acute phase reactants. No changes in C3d and C reactive protein were seen after treatment with fresh frozen plasma.

Most of our patients with suspected infection had low plasma concentrations of fibronectin, which acts as a negative acute phase reactant during infection. Fibronectin concentrations did not change after infusion with either fresh frozen plasma or immunoglobulin, in contrast with the study of Calioli et al.

Comparing the concentrations of humoral immune components in fresh frozen plasma and immunoglobulin, it is apparent that the higher IgG content in the latter is responsible for the significant increase in total IgG and its subclasses. To achieve the concentrations of IgG provided by immunoglobulin, an infusion of 30–50 ml/kg of fresh frozen plasma would be required, an unacceptable volume in these infants.

Although it has been suggested that intravenous immunoglobulin treatment is more beneficial in infants of less than 34 weeks’ gestation and less than 1500 g birth weight, we did not observe any difference in the effects of intravenous immunoglobulin on markers of humoral immunity in very premature infants compared with those of older gestational age. We are aware of only one previous study of the effects of fresh frozen plasma on the immune function in neonates. This study suggested that fresh frozen plasma enhances neonatal neutrophil motility by providing complement and fibronectin, facilitating movement of these cells to sites of infection. The study did not include control subjects, however, and although the enhancement of neutrophil motility was attributed to complement factors and fibronectin in the fresh frozen plasma, these components were not measured. To our knowledge, our study is the first to show that there are few effects on humoral immunity after fresh frozen plasma administration in neonates, and those changes that occur are of questionable benefit to the host.

Despite the paucity of definitive indications for its use, the administration of fresh frozen plasma in the past several years has been widespread. Although well defined indications exist for the use of fresh frozen plasma in single or multiple coagulation deficiencies, indications for many of its other uses are empirical. A study by Strauss et al. surveying neonatal transfusion practices showed that most respondents (77%) transfused fresh frozen plasma appropriately – that is, primarily to treat coagulation disorders. Eight per cent, however, stated that their most frequent use of fresh frozen plasma was solely to treat sepsis, a practice questioned by the results of this study. The key opsonins contained in antibody of the IgG class do not appear to be administered using fresh frozen plasma. More importantly, fresh frozen plasma, despite donor selection and screening procedures, still carries the risk of viral transmission because the process of preparation does not eliminate or inactivate viral contaminants. This complication is less likely with intravenous immunoglobulin which uses ethanol fractionation for viral inactivation.
The results of this study suggest that fresh frozen plasma treatment is less effective than intravenous immunoglobulin for the provision of components of humoral immunity which are important in neonatal infection. The optimum dose, administration time and dosage intervals, potential toxicity, and clinical relevance of either treatment remain to be clarified. In addition, for the potentially infected neonate, alternative means of achieving improved immunity need to be studied. These might include cytokine treatment aimed at increasing granulocyte production and function, or fibronectin treatment to foster neutrophil adherence and opsonisation. These methods might profitably be combined with immunoglobulin treatment, but not, it seems, with fresh frozen plasma.

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