Treatment of sepsis with IgG in very low birthweight infants

Despite the continued development of new antibiotics with increased ranges of activity and spiralling prices, sepsis—either acquired from the mother intrapartum or acquired nosocomially from invasive procedures—remains a serious problem in preterm infants. All neonatologists must have witnessed infants dying of septicaemia despite treatment with an antibiotic to which the organism was sensitive in vitro. The problem is largely one of host defence. Infants born before 32 weeks’ gestation are seriously immunodeficient with cord blood concentrations of IgG being less than half those found in babies born at full term. Concentrations of IgA and IgM are negligible in cord blood. In addition, very preterm infants have reduced complement factors, opsonic activity, polymorphonuclear chemotaxis, and are liable to exhaust their neutrophil storage pools.1

As IgG is acquired across the placenta, and the infant produces virtually none of its own for months, serum IgG concentrations decline from birth for six to eight weeks reaching 1–2 g/l between 2 and 4 months of age; these low concentrations must be of functional importances. Opsonisation of important capsulated perinatal pathogens such as group B streptococci, *Escherichia coli* and *Staphylococcus epidermidis* is facilitated by specific antibody.2 Release of marrow neutrophils is accelerated by type specific antibody,3 which also speeds up migration of neutrophils into the infected tissue.4

Accepting that infants born at less than 32 weeks’ gestation have clinically important immunoglobulin deficiency, can they be effectively and safely treated with replacements? What preparations are suitable? What size of dose and number of doses are required? What is the evidence of efficacy?

Immunoglobulin preparations

Early preparations of human gammaglobulin were not suitable for intravenous injection because of the presence of impurities and aggregated immunoglobulin, which gave rise to complement activation and anaphylaxis. The early preparations could safely be given intramuscularly but insufficient volume could be injected to raise the serum concentrations of IgG to those of a full term infant. Highly purified human immunoglobulin suitable for intravenous use has been available for the last decade. Sandoglobulin (Sandoz), is one of the most widely used in Europe. It is a Swiss Red Cross pooled polyvalent IgG concentrate produced by alcohol cryoprecipitation and mild acidification at pH 4 from plasma known to be negative for hepatitis B antigens and antibodies to HIV. Gammagard (Baxter Health Care), Intraglobin (Biotest Pharma), and Venogamma Polivalente (Ismunit) are also IgG concentrates made by ethanol fractionation of plasma. An IgM enriched immunoglobulin has recently been developed (Pentaglobin, Biotest Pharma). A dose of 250 mg of protein in 5 ml contains 190 mg IgG, 30 mg of IgM, and 30 mg of IgA.

Dosage

Chirico et al showed that 500 mg/kg Sandoglobulin given to preterm infants under 1500 g raised the mean serum IgG concentration to over 13 g/l, with a serum half life of 260 hours.3 Antibody titres to *E coli* rose to a concentration that is normally protective, and with a serum half life of 112 hours. Antibody titres to group B streptococcus rose to normally protective concentrations with a serum half life of 82 hours, and antibody to cytomegalovirus also rose appreciably with a serum half life of 112 hours. Noya et al studied pharmacokinetics of Gammagard in 20 infants weighing 750–1500 g during the first week.6 Mean IgG rose from around 5 g/l to over 13 g/l (equal to the concentrations in full term infants or adults) 15 minutes after infusion of 500 mg/kg. Mean IgG had fallen to 7·3 g/l by 7 days, to 6·1 g/l by 14 days, to 5·1 g/l after 21 days, and to 4·3 g/l after 28 days.

Toxic effects

No liver damage or anaphylaxis has been reported in newborns. The theoretical possibility that administration of IgG early in life might suppress later development of endogenous IgG was investigated by Sidiropoulos.7 He followed up a group of infants treated with Sandoglobulin in the neonatal period and found normal serum concentrations of IgG and antibodies to tetanus toxoid at 4 years of age. Ethanol fractionation of plasma has been shown to inactivate HIV.8

Efficacy

IgG replacement may be carried out prophylactically in infants at high risk of sepsis (for example <32 weeks’ gestation, <1500 g in weight) or as ‘rescue’ treatment in infants already ill with sepsis. Four randomised trials of prophylaxis have been published. Haque et al randomised 150 preterm infants in Saudi Arabia into three groups of 50; one group received a single infusion of 120 mg/kg of Intraglobin on day 1, a second group received two such infusions, the first on day 1 and the second on day 8, and the third (control) group received no immunoglobulin.9 Culture positive infections (five septicaemia, two meningitis, and one salmonella gastroenteritis) developed in eight infants (16%) of the control group and in four (4%) in the two immunoglobulin treated groups (four with septicaemia). This difference in incidence of sepsis is significant. Although 120 mg/kg is a smaller dose than that used by most other investigators, Haque et al found a satisfactory rise in serum IgG.

In another prophylactic trial, 500 mg/kg of Sandoglobulin was given intravenously weekly for one month to infants weighing less than 1500 g in a randomised open trial (83 infants).5 Only two of the treated infants (5%) developed septicaemia compared with eight of the control group (20%). Of the control group 15% died with infection as the main cause, compared with 2% of the treated group. The same investigators carried out a prophylactic trial in infants over 1500 g who were receiving intensive care and found no difference in outcome.5

Stabile et al carried out an open randomised prophylactic trial in which they gave 500 mg/kg of Venogamma Polivalente on the first, second, third, seventh, 14th, 21st, and 28th days in 94 preterm infants with a mean gestational age of 31 weeks and a mean birth weight of 1340 g.10 They
found no difference in the incidence of sepsis or mortality between the two treatment groups. The results of this trial are perhaps not directly applicable to very preterm infants in other countries because many of the infants were over 1500 g or 30 weeks, the range of organisms was unusual with not a single case of group B streptococcus or E coli, and the immunoglobulin preparation is different from that used in all other neonatal studies and is not available in most countries. Didato et al carried out a prophylactic trial of intravenous IgG but with insufficient statistical power (only 37 infants under 1500 g); no significant difference was found.11

Sidiropoulos et al carried out a randomised open ‘rescue’ trial in infants ill with suspected sepsis.12 Sandoglobulin was given to half the preterm infants in a dose of 500 mg/day for a total of six days. Sepsis was confirmed in 22 preterm infants. Four out of nine preterm infants in the control group and one out of 13 preterm infants in the group receiving immunoglobulin died (p<0·04).

Haque et al carried out a double blind ‘rescue’ trial.13 Sixty infants ill with suspected sepsis (later confirmed in 44) were randomised and 250 mg/kg Pentaglobin was given daily to half the infants. Mortality from sepsis was significantly higher, being six out of 30 (20%) in the control group, and one out of 30 (3%) in the immunoglobulin treated group.

Conclusion

The published evidence shows a pronounced, prolonged deficiency of immunoglobulin in very preterm infants, which places them at increased risk of bacterial sepsis. Highly purified and apparently safe intravenous immunoglobulin preparations can restore serum IgG concentrations to those of full term infants or adults. Two out of four randomised trials concluded that prophylaxis could reduce septicaemia in infants weighing <1500 g and two ‘rescue’ trials have shown improved survival in septic neonates. Large randomised trials are in progress in the United States. Whether neonatologists opt to use IgG prophylactically in the highest risk group (those weighing under 1000 g receiving intensive care) will depend on the background incidence of bacterial sepsis in their own neonatal units. There are other ways of reducing the incidence of sepsis, such as recruiting adequate numbers of qualified nurses, strict handwashing, and avoidance of invasive procedures.

Further research is needed on the minimum effective dosage and the interval between doses, but in units where infection is common in very low birthweight infants it is reasonable (on available data) to treat prophylactically with 500 mg/kg on admission and to repeat treatment every one to two weeks. In the absence of hypovolaemia, IgG should be given slowly over three hours, as the volume of Sandoglobulin is 17 ml/kg with 2·5 mmol of sodium/kg. In the United Kingdom, Sandoglobulin costs £19·50 for 1 g and £46·80 for 3 g. We have found that treating two or three infants out of the same bottle on the same day reduces the cost to acceptable levels. Alternative approaches would be to monitor serum concentrations of IgG weekly in infants weighing under 1500 g and treating infants whose concentrations fell below 3·0 g/l,14 or to reserve IgG for immediate use in very low birthweight infants who became ill with suspected sepsis. Whichever policy is adopted, IgG will not protect against all types of infection. Fresh frozen plasma is also required to restore complement dependent opsonisation fully. In the future, human monoclonal antibody preparations against the common perinatal pathogens will probably provide more effective treatments in smaller volumes of fluid.15 The increasing numbers of very preterm infants being treated with dexamethasone for bronchopulmonary dysplasia are likely to have decreased cell mediated immunity as well as immunoglobulin deficiency.

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