CONTINUING MEDICAL EDUCATION

ROLE OF INTRAVENOUS IMMUNOGLOBULIN IN PREVENTION AND TREATMENT OF NEONATAL INFECTION

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Passive immunity for temporary protection against infections dates from the 19th century. Earlier preparations, such as animal sera, human convalescent serum, human serum immune globulin (HISG) had their own disadvantages(1) Accordingly several pharmaceutical companies developed human gamma globulin suitable for intravenous use (*Table I*)(2).

Pharmacology of Intravenous Immunoglobulin (IVIG)

An ideal IVIG preparation should contain structurally and functionally intact immunoglobulin molecules with normal biologic half-lives and a normal proportion of immunoglobulin subclasses. The preparation should also contain high levels of antibodies relevant to its proposed use and should contain no vasomotor peptides, endotoxin or infectious agents(2). There are substantial differences in methods of preparations of IVIGs that may affect their functional antibody activity.

Each lot of IVIG has its own characteristics with reference to specific antibody titres. Most preparations contain 250 mg protein in 5 ml which includes 190 mg IgG, 30 mg IgA and 30 mg IgM. The half lives (T ½) of most preparations is 18 to 32 days in adults while in neonates it is variable(3). The mean T ½ in neonates is approximately 22.6 ± 5.9 days and is influenced by birth weight (387 hours in babies less than 1 kg to 683 hours in babies > 1.5 kg)(4,5). It also increases with postnatal age, significantly more so in babies who were less than 1 kg at birth(6).

IVIG is used in generalised or partial antibody deficiencies of congenital or acquired origin, selective antibody deficiency in otherwise immunocompetent individuals or for modification of immune system.

Prophylaxis

Prophylactic use of IVIG is to be considered mainly in preterms, small for date or in other high risk infants where there is increased risk of infection due to incomplete acquisition of maternal antibodies, sluggish antibody response to antigens, physiologic hypogammaglobulinemia, im-

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TABLE I--*Commercially Available IVIG Preparations*

Product name	Manufacturer
Gammaonativ	Kabi Vitrum AB, Sweden
Gamimmune N	Cutter Biological, California (USA)
(Polyglobin N)	
Sandoglobulin	Sandoz A G, New Jersey (USA)
Globulin N	Armour, New York (USA)
Intraglobin F*	Biotest Pharma, West Germany
Pentaglobin*	-do-
Venimmune	Behrinwerke AG, West Germany
Iveegam	Immuno A G, Austria
Gammagard	Baxter Health Care Corpn., Hyland Division, California (USA)

(* Available in India)

mature complement and phagocytic system. Intramuscularly used HISG for prophylaxis against infection in preterm is not beneficial because of its uneven absorption, slow availability, tissue damage and pain with resultant problems in administering adequate amounts(7,8)

IVIG has been shown to have opsonic activity *in vitro* against a variety of bacterial pathogens including Group B streptococci and *E. coli*. Several animal studies have shown that IVIG containing specific opsonic antibodies has a protective role(9).

A short study at our Centre revealed that immunoglobulin supplementation *in vitro* at concentration of 5 g/dl significantly enhanced the opsonic and phagocytic activity of neonatal serum against *Staphylococcus aureus* in both prematures and IUGR neonates and hence IVIG may have some role in antibacterial host defences(10).

There are 7 studies in literature evaluating efficacy of IVIG in preventing neonatal infections (*Table II*). These reports, however should be interpreted cautiously. Studies by Haque *et al.*(11) and Chirico *et al.*(12) lacked proper statistical analysis while the other studies had inadequate sample sizes, limiting the conclusions for prophylactic efficacy(13).

Therapeutic Use

Over the past decade, through advances in our understanding of the role of type specific antibody in protection of the newborn infant against invading organisms, particularly Group B streptococci, IVIG has evolved as one of the modes of immunotherapy(14,15).

Fischer *et al.*(14), Sideropoulos *et al.*(16) and Haque *et al.* (17) have reported the efficacy of IVIG in the treatment of neonatal sepsis. However, Kim has refuted these studies because of improper statistical analysis(18).

Recommendations for Use of IVIG(19,20)

1. IVIG preparations in newborn have been shown to be safe by follow up studies till 3 years of age, in doses as high as 1300 mg/kg, though one cannot disregard the potential for adverse reactions (21).
2. Administration of IVIG should be done

TABLE II — *Studies on IVIG in Neonatal Septicemia*

Author & year of publication	Preparation and schedule	Characteristics of patients	Types of sepsis and organisms	Conclusions & remarks
Prophylactic				
1. Heaque KN (1986)(11)	Intraglobin F. (Biotest Pharma, WG) 120 mg/kg on D_1 (Group A), D_1 and D_8 (Group B)	50 infants in each group (A&B) vs 50 controls Gestation age 30-36 weeks. B.Wt. 0.9-1.5 kg	Early onset sepsis; Mean onset 46.3 h (8-76 h); *E. coli*, Salmonella, Klebsiella, Serratia	1. Nonblinded study 2. The incidence of sepsis is significantly lower in the treated group ($p<0.001$) 3. The mortality from sepsis is significantly lower in the treated group ($p<0.001$) 4. The rise in IgG from 150 mg/dl to 650 mg/dl on day 8 & 1700 mg/dl on day 12 in study group 5. No side effects noted
2. Chirico G (1987)(12)	Sandoglobulin (Pepsin treated obtained at pH 4 (Sandoz). 500 mg/kg weekly for one month.	43 infants vs 40 controls. Gestation age 24-34 weeks, B.Wt. 640-1470 g	Late onset sepsis Age of onset not mentioned Organisms not mentioned	1. Non blinded, not placebo controlled study 2. Significant reduction in the incidence of infection ($p<0.02$), septicemia ($p<0.05$) and sepsis related deaths ($p<0.04$) in treated group 3. No reduction in duration of antibiotics and stay in hospital 4. Half life of IgG in preterm 260 h, antistreptococcal IgG 82 h, anti-*E.coli* IgG 160 h, anti-CMV IgG 112 h 5. No difference in mortality, stay in hospital, antibiotic duration and ventilator dependency in treated group more than 1.5 kg 6. Gamma globulin therapy more effective in preventing generalized than localized infection

continued

Author & year of publication	Preparation and schedule	Characteristics of patients	Types of sepsis and organisms	Conclusions & remarks
3. Stable A. (1988)(22)	Venogamma Polivalente (Ismunit, Italy) 0.5 g/kg IV D 1,2,3, 7,14, 21 and 28	44 vs .40 controls Gestation age 26-34 weeks, B.Wt. 870-1790 g	Late onset sepsis Range 2-25 days *Staph. epidermoidis,* Klebsiella, Serratia, *Staph. aureus* *P. aeruginosa*	1. 0.5 g/kg sufficient to raise IgG above 8 g/L 2. The incidence of proven and probable sepsis, mortality related to sepsis in first 40 days of life, not significant in treated group ($p > 0.01$), also incidence of minor infections not significant in the same group ($p > 0.05$) 3. Tolerance of product excellent
4. Bussel JB (1988)(23) (Abstract)	1 g/day on D 1,2,3,4 and 15	50 vs.56 controls B.Wt. 700-1300 g	Late onset sepsis (continued till 2 months)	1. The incidence of proven sepsis significantly reduced in treated group ($p < 0.05$). However, the difference did not persist till 2 months
5. Baker, CJ (1989)(24) (Abstract)	Gammagard 500 mg/kg D 3-7 and 1 week later followed by 14 days interval till total 5 doses	176 vs. 185 controls B.Wt. 500-1750 g	Late onset sepsis 75% Gram positive organisms	1. Proven sepsis significantly reduced in treated group ($p < 0.0015$) 2. Significant reduction in incidence of NEC ($p < 0.04$) 3. Incidence of infection not affected in >1.5 kg neonates
6. Clapp DW. (1989)(25)	Sando-globulin 500 mg/kg <1 kg. 700 mg/kg >1 kg. every 2 weekly dose increased by 200 mg/kg to maintain 700 mg/dl IgG in serum	56 vs. 59 controls B.Wt. 600-2000 g Mean Gest. age 30-31 wks	Late onset sepsis Range 6-131 days Staph. coagulase +ve, *Candida albicans,* *Staph. aureus,* *H. influenza* (non-typable)	1. Incidence of proven sepsis significantly lower in treated group ($p < 0.01$), while probable sepsis not significantly different 2. No side effect except one developed transient hypotension 3. No NEC difference in treated group

Author & year of publication	Preparation and schedule	Characteristics of patients	Types of sepsis and organisms	Conclusions & remarks
7. Conway SP (1990)(26)	Intraglobin F (Biotest Pharma, FRG) 200 mg/kg IV every 3 weekly 100 mg/kg on suspicion and another dose on confirmation of of sepsis to babies in treatment group	29 vs. 26 controls Gest. age 27.5 weeks ± 1.4 weeks, B.Wt. 1088 ± 233 g	Late onset sepsis Range: Not mentioned Coagulase –ve Staphylococci, *Staph. aureus,* *P. aeruginosa,* Candida sp.	1. Randomised, not placebo controlled, not blinded 2. Incidence of infection in treated group lesser than in controls, however, the difference is significant only when probable sepsis is included to culture proven sepsis for analysis ($p=0.01$) 3. The median levels in treatment (IgG) group at 3 weeks and 6 weeks were 6.0 g/L and 4.18 g/L, respectively 4. The babies in treatment group had lesser stay in ICU ($p=0.001$)
Therapeutic				
1. Haque (1988)(17)	Pentaglobin (Biotest pharma, F.R.G.) 250 mg/kg/day for 4 days	30 vs. 30 controls Gest. age 28-37 weeks B.Wt. 0.9-1.7 kg	Early onset sepsis Range 18-96 h *E. coli,* Salmonella, Klebsiella sp, *Staph. epidermidis.*	1. Randomised placebo controlled, not blinded 2. Mortality in treated group significantly reduced ($p<0.001$) 3. No side effects except mild hemolysis 4. Difference in mean IgM level was significant on day 7 and 10 but not in IgG levels

Gest. = Gestation; B.Wt. = Birth weight

over 3 hours at a rate not exceeding 0.1 ml/kg/min.

3. The screening of all commercial plasma collected for IVIG preparations for HIV and hepatitis B and alcohol fractionation have virtually eliminated the risk of transmission of viruses.
4. For prophylaxis one can adopt one of the following approaches:
   (*a*) To treat all very low birth weight (VLBW) babies (<1.5 kg) with 500 mg/kg on admission and to repeat infusions every fortnight.
   (*b*) To monitor serum concentration of IgG weekly in VLBW babies and treat those when the levels fall below 3 g/L (300 mg/dL). Use of IVIG as a prophylactic or therapeutic modality cannot be recommended in infants greater than 1.5 kg or those >34 weeks post conception, at present.
5. In VLBW babies and in extreme prematurity therapeutic efficacy of IVIG in neonatal sepsis is not clear.

Thus the use of IVIG prophylactically in high risk neonates will depend on the incidence of bacterial sepsis in the nurseries. IVIGs are not to be used as a last resort in therapy but early and judiciously when indicated. Directed immunoglobulin preparations are more likely to be effective against specific bacterial pathogens. The research in monoclonal and antiendotoxic antibodies will probably provide more effective ways of management of neonatal sepsis in the future.

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