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ORIGINAL ARTICLE

Is there enough evidence for the use of immunoglobulins in either prevention or treatment of bacterial infection in preterm infants?

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Abstract The incidence of infection is higher in the neonatal period than at any other time of life, and factors that determine this increased susceptibility to bacterial infection include low levels of immunoglobulins especially in the preterm infant. Longitudinally determined plasma immunoglobulin concentrations of preterm infants are lower compared to term infants.

Studies so far revealed IVIG administration for the prevention of neonatal sepsis being safe resulting in a 3 to 4 percent reduction in nosocomial infections with no significant effect on mortality by meta-analyses. This marginal positive effect has to be discussed in the light of the costs and the values assigned to the clinical outcomes. There is not enough evidence for the use of immunoglobulins in the treatment of bacterial infection in preterm infants. IgM enriched IVIG might be beneficial for extremely low gestational age newborns but up to now meta-analyses do not support its general use in neonates.

Introduction

The incidence of infection is higher in the neonatal period than at any other time of life, and factors that determine this increased susceptibility to bacterial infection include on the one hand the

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immaturity of the immune system with poor humoral responses to organisms (IgG and A), relatively poor neutrophil responses and complement activity, impaired macrophage function, and relatively poor T cell function, and on the other hand the exposure to microorganism from the maternal genital tract by ascending infections via the amniotic fluid or trans-placental hematogenous spread. Additionally peripartum factors like trauma to skin or vessels during parturition or exposure to invasive obstetric procedures as well as portals of colonization and subsequent invasion (umbilicus, mucosal surfaces, eye, and skin) contribute to this increased risk for bacterial infection (Isaacs and Moxon, 1999).

In a National Institute of Child Health and Human Development Neonatal Research Network study including 6093 extremely low birth weight infants at least 65% had one or more infections during their hospitalization (Stoll et al., 2004). Infants were followed-up at 18—22 months of corrected gestational age and compared with uninfected infants infected infants were significantly more likely to have adverse neurodevelopmental outcomes including cerebral palsy, low Bayley Scales of Infant Development II scores on the mental development index and psychomotor development index, and vision impairment. Infection in the neonatal period was also associated with impaired head growth, a well-known predictor of poor neurodevelopmental outcome.

Additional factors associated with greater susceptibility to bacterial infection of preterm infants include invasive procedures during their stay at the NICU, prolonged artificial ventilation, intravenous feeding and antibiotic pressures (Isaacs and Moxon, 1999). The incidence is estimated to range from 1 to 5—8.1 per 1000 live births (Isaacs and Moxon, 1999; Gerdes, 2004). Every year an estimated number of 4 million babies die within the first four weeks of life, and, globally, the main direct causes of neonatal death were estimated to be preterm birth, severe infections, and asphyxia with 28, 26, and 23 percent, respectively (Lawn et al., 2005).

Aim of this review was to elucidate the evidence for the use of immunoglobulins in the prevention and the treatment of neonatal bacterial infection of the preterm infant.

The innate immune response and the role of immunoglobulins

Humoral immunity of the human newborn is primarily provided by maternal immunoglobulin G (IgG) that starts being transferred transplacentally at 8—10 weeks of gestation and accelerates during the last trimester. Premature infants, compared to full-term infants, have lower levels of IgG at birth that further decreases during the first few weeks of life (Jenson and Pollock, 1997). The relative deficiency of humoral immunity in premature newborns contributes to the inverse correlation of birth weight with the rate of neonatal sepsis. An 86-fold increased rate of sepsis in newborns of birth weights ranging from 600 to 999 g compared to newborns of birth weights above 2500 g has been reported (Jenson and Pollock, 1997).

Ballow et al. (1986) longitudinally determined plasma immunoglobulin concentrations of preterm infants weighing less than 1500 g from birth up to 10 months of chronological age. During the first week of life plasma IgG levels correlated well with gestational age. At the age of three months mean plasma IgG levels were 60 mg/dl in infants of 25—28 weeks of gestation and 104 mg/dl in infants of 29—32 weeks of gestation. Most infants had hypogammaglobulinemia at six months with plasma IgG levels below 200 mg/dl. Plasma IgM concentrations were low in both groups during the first week of life and increased by eight to ten months of life. IgA concentrations were comparable for both groups during the first week of life. After discharge 43 preterm infants were followed until ten months of chronological age and a significantly higher incidence of infections was observed compared to 41 term infants.

The probability of developing infection due to group-B streptococci (GBS) type Ia declined with increasing maternal levels of IgG GBS Ia antibodies (Lin et al., 2001). A maternal antibody level $\geq$5 mg/mL resulted in an 88% lower risk of developing type-specific early-onset disease. Interestingly, intravenous immune globulin (IGIV) alone did not consume complement and showed no opsonic activity by itself for polymorphonuclear leukocyte membrane receptor mediated phagocytosis of *Staphylococcus epidermidis, Klebsiella pneumoniae*, and groups A and B streptococci (Yang et al., 1989). When these bacteria were pre-opsonized in IVIG, significant amounts of complement were consumed and the uptake and killing of bacteria occurred. An important finding was the fact that in vitro opsonic activity of IGIV for these organisms was significantly correlated with the amount of complement consumed by the IVIG — opsonized bacteria. The in vivo protective efficacy of IVIG also appeared to be directly associated with its ability to activate and consume complement. The higher the titers of the IVIG preparation were the more opsonic activity was shown towards slime-producing *S. epidermidis* (Lamari, 2000).