Intravenous Immunoglobulin in Neonatal Sepsis

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Abstract

Neonatal sepsis remains the major cause of mortality and morbidity including neurodevelopmental impairment and prolonged hospital stay in newborn infants. Despite of advances in technology and optimal antibiotic treatment, incidence of neonatal sepsis and its complications remains unacceptably high especially in developing countries. Premature neonates in particular are at higher risk due to developmentally immature host defense mechanisms. Though not approved by Food and Drug Administration (FDA) U.S.A, off label use of intravenous immunoglobulin continues in many countries. Recent evidences showed no significant decrease in the mortality rate or other outcomes when intravenous immunoglobulin is administered in addition to standard therapies. Hence, use of intravenous immunoglobulin in suspected or proven neonatal sepsis is not recommended. The expense of prophylactic use of intravenous immunoglobulin administration for both term and preterm newborn population, given the minimal benefit is not justified. Future studies are required which should focus on other prophylactic or adjuvant treatment modalities in addition to the standard therapy in neonatal sepsis.

Introduction

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life. Sepsis occurring in the first 72 hours of life is defined as early-onset sepsis (EOS) and that occurring beyond 72 hours as late-onset sepsis (LOS). Neonatal early onset sepsis is defined by Centers for Disease Control and prevention (CDC) as blood or cerebrospinal fluid culture proven infection occurring in the newborn younger than 7 days of age. Neonatal late onset sepsis is usually defined as a culture-proven systemic infection in an infant between seven days and three months of age. For hospitalized VLBW infant, EOS is defined as culture-proven infection occurring at fewer than 72 hours of age. Incidence of neonatal sepsis varies from 2.2/1000 live births in developed countries to 10-50/1000 live births in developing countries; though under reporting is common in both. In China the incidence of neonatal sepsis accounts for 1%-10% of all neonates requiring medical attention and 13%-50% of all neonatal mortality cause. The incidence of neonatal sepsis in India according to National Neonatal Perinatal Database is 30/1000 live births. Sepsis has been reported as cause of neonatal death in 20-50% cases in community based studies. There is no national database mentioning incidence of neonatal sepsis in Nepal till date. Deaths occurring in the neonatal period each year account for 41% (3.6 million) of all deaths in children under five years of age.

In Nepal, out of the total infant mortality rate of 46/1000 live births, more than two-third, i.e. 33/1000 live births is contributed by neonatal mortality. Both the incidence of sepsis, 1/230 live births versus 1-5/1000 live term births and mortality from sepsis between 18-20% remain unacceptably high in VLBW preterm infants.

Intravenous immunoglobulin

It has been more than 60 years since Ogden C. Bruton’s reported use of human- plasma-derived IgG of an 8-year-old boy with agammaglobulinemia. IVIg has now become an important treatment option in a number of clinical indications beyond primary immunodeficiency,
including autoimmune and acute inflammatory conditions\textsuperscript{12}. Off-label prescribing has crossed over into almost every medical specialty including neonates.

Endogenous immunoglobulin synthesis does not begin until 24 weeks of life; young infants rely on in-utero maternally acquired immunoglobulins for protection against systemic infection. The placental transfer of these protective antibodies, however, does not occur until week 32 of gestation and post-natally IgG levels decrease due to reduced production in newborns. The administration of intravenous immunoglobulin (IVIg) may improve immune function by providing IgG that can bind to cell surface receptors, provide opsonic activity, activate complement, promote antibody dependent cytotoxicity, and improve neutrophilic chemokines. However, there remains an ongoing debate about the efficacy of IVIg in the treatment of neonatal sepsis\textsuperscript{13}.

**IVIg prophylaxis and adjuvant therapy**

The first four studies published in 1981, 1986, 1988 and 1989 showed an increased risk of death in septic neonates given antibiotics but not treated with IVIg, compared to children given antibiotics plus IVIg, signifying the importance of IVIg as useful adjunctive therapy. The prophylactic role of IVIg was first studied in 1986 and 1987, which showed a benefit from the use of IVIg to prevent proven bacterial sepsis\textsuperscript{14}.

Various small single center clinical trials in mainland China have shown beneficial effects of use of IVIg in suspected or proven neonatal sepsis, especially premature infants\textsuperscript{15-17}. On the contrary few recent trials have shown no effect of IVIg in prevention and treatment of neonatal sepsis in premature infants\textsuperscript{18, 19}. The effectiveness of IVIg preparations in the prevention or treatment of neonatal sepsis remained uncertain, due in part to studies that included relatively small or heterogeneous populations. Internationally there have been various studies with contradictory results. In 1994 first large clinical trial was done. The National Institute of Child Health and Human Development Neonatal Research Network published the largest randomized clinical trial (n=2,416) assessing the role of IVIg in the reduction of premature neonatal sepsis. The prophylactic administration of IVIg in this study did not reduce the incidence of nosocomial infections, morbidity and mortality in premature infants\textsuperscript{20}.

In the past 10 years, many systematic reviews and clinical trial results were published. In 2004 a systematic review by Cochrane collaboration evaluated the relationship between IVIg therapy and all-cause mortality during hospitalization in premature and term infants. Combining the results of 7 studies (n=262), treatment with IVIg in cases of culture-proven infection resulted in a reduction in all-cause mortality (RR 0.55; 95% CI 0.31, 0.98)\textsuperscript{21}. The authors did not observe between-study heterogeneity; however, (especially in a setting when fewer than 20 studies are analyzed), and the studies were different in the variety of IVIg products, different dosing regimens, and patient populations. In 2006 a multicenter (20 sites), randomized, double blinded, placebo controlled study evaluated the safety and efficacy of 2 infusions (14 days apart, dose = 1000 mg/Kg) of an anti-staphylococcal IVIg (Altastaph) in VLBW infants. The product was determined to be safe among the intervention group (n=104); however, when compared to placebo (n=102) no change was observed in the cumulative incidence of invasive staphylococcal infections\textsuperscript{22}.

In 2007, another multicenter, randomized clinical study involving 95 sites in the US and Canada evaluated the effect of up to 4 infusions of INH-A21 (Veronate, dose = 750 mg/Kg dosed on days 1, 3, 8 and 15), an anti-staphylococcal IVIg (anti-clumping Factor A and anti-Ser-Asp dipeptide repeat G), on the prevention of Staphylococcal late-onset sepsis among 1,983 infants with birth weights <1,250 g who received at least one infusion of study drug or placebo (989 vs. 994, respectively). In this study, no difference was observed between treatment groups in frequency of Staphylococcus aureus infections, 5% for INH-A21 vs 6% for placebo\textsuperscript{23}. Pagibaximab, an anti-staphylococcal monoclonal antibody (anti-lipoteichoic acid) administered in 3 doses (7 days apart, 60 to 90 mg/kg/dose), was evaluated in a randomized, placebo controlled phase II study in infants with birth weight <1,300 g (n= 88). A trend was observed in the reduction of Staphylococcal bloodstream infections; none of the subjects in the 90 mg/kg group had confirmed staphylococcal sepsis compared to 20% and 13% in the 60 mg/kg and placebo groups, respectively (P<0.11)\textsuperscript{24}.

In 2010, Khalid N.Haque did a pragmatic review of 14 studies published within 1970 to 2010. The primary and only outcome parameter measured for this study was the impact of immunoglobulin therapy on mortality from neonatal sepsis. Analysis of 14 studies revealed a reduction of 48% in all cause mortality associated with neonatal sepsis when IVIg was used as an adjunct to standard therapy (OR 0.52; 95% CI 0.40-0.67)\textsuperscript{25}. In the same year, Cochrane updated its previous review of intravenous immune globulin for infection in neonates with suspected or subsequently proven infection. It included 10 trials of variable quality undertaken in eight countries\textsuperscript{26}. Mortality was reduced among patients with clinically suspected infection in 7 trials involving 378 infants (relative risk, 0.58; 95% CI, 0.38 to 0.89) and among patients with subsequently proven infection in 7
trials involving 262 patients (relative risk, 0.55; 95% CI, 0.31 to 0.98). Because of concerns about study quality, there was still insufficient evidence to support the routine administration of IVIg to prevent mortality in infants with suspected or subsequently proved neonatal infection. A large study of the effectiveness of IVIg in neonates with suspected infection had recently been completed. Results of the International Neonatal Immunotherapy Study (INIS trial)\(^{27}\), which enrolled 3,493 infants, were expected to establish the usefulness of IVIg for suspected infection in newborns.

**Latest Clinical Evidence**

In 2011, the outcome of multicenter clinical trial organized by International Neonatal Immunotherapy Study (INIS) Collaborative Group was published. The trial enrolled 3,493 infants receiving antibiotics for suspected or proven serious infection in the multicenter clinical trial at 113 hospitals in nine countries and randomly assigned to receive two infusions of either polyvalent IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years. The multicenter trial by INIS collaborative group showed no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1759 infants (39.0%) who received intravenous immune globulin and in 677 of 1734 infants (39.0%) who received placebo (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or non major disability or of adverse events\(^{27}\).

In 2012, systematic review with meta-analysis by Andréia C. B. F. Franco et al evaluated seven RCTs for the mortality rate, including 3,756 patients. The global effect of this outcome showed no statistically significant difference between the groups\(^{28}\).

**Conclusion**

The development of IVIg has been a great achievement in medical history. But its use should be clinical evidence based. Latest evidence showed no significant benefits of IVIg use in neonatal sepsis. For the developing countries like Nepal, where the constraint for use of IVIg is its cost and availability, this result should come as a relief. In addition, prevention of ineffective expensive treatment therapy can save millions of dollars. Studies on other adjuvant therapies such as colony stimulating factors, probiotics, glutamine supplementation and lactoferrin have been tested with mixed results. In future, further large randomized clinical trials should evaluate the effectiveness of other adjuvant or prophylactic therapies for suspected or proven neonatal sepsis which may result in significant decrease in neonatal mortality and morbidity.

**References**


