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Research Article

Efficacy of intravenous immunoglobulins in the prophylaxis of neonatal sepsis

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Summary

Despite critical care advances, robust antibiotic therapy and improved strategies in early detection and prevention of infection, the incidence of morbidity and mortality from neonatal sepsis worldwide in preterm and low birth weight neonates remains overwhelmingly high. Neonatal sepsis is characterised by a clinical syndrome of systemic signs of infection and bloodstream bacteraemia in newborns within the first months of life.

The risk of sepsis in neonates is inversely proportional to gestational age and birth weight due to deficiency in humoral immunity and the need for more invasive supportive neonatal intensive care unit interventions. Adverse effects such as necrotising enterocolitis associated with antimicrobial therapy are serious enough to warrant exploration of alternative therapeutic strategies. Immunoglobulin replacement therapy offers hope of enhancing immune competence and reducing infection rates in vulnerable populations.

It is evident from the relevant studies to date that the benefits offered by intravenous immunoglobulin prophylaxis may not be significant enough for routine hospital implementation. Further research to better understand the mechanisms underlying immunodeficiency will lead to the realisation of alternative therapeutic and prophylactic interventions.

More Information

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Introduction

37% of neonatal deaths in 2010 were attributable to infectious causes [1]. Preterm neonates are particularly susceptible due to numerous factors including the requirement of more invasive supportive interventions in the Neonatal Intensive Care Unit (NICU) as well as an inherent deficiency of humoral immunity [3].

Between weeks 30-32 of gestation, intrauterine transplacental transfer of maternal immunoglobulins (IgG) to the fetus accelerates, conferring passive immunity [7]. There is an incremental rise in foetal IgG with gestational age, thus preterm and low birth weight neonates are born with a true deficiency of IgG antibodies [7]. As low serum IgG has been reported to increase the risk of infection, IgG replacement therapy offers hope of enhancing immune competence and decreasing infectious episodes in this vulnerable population [8].

This paper is a review article that aims to evaluate all relevant research to date regarding prophylaxis of neonatal sepsis by intravenous IgG replacement therapy in preterm and low birth weight neonates.

Methodology

Articles were searched using the following databases: ScienceDirect, Medline, PubMed, Google Scholar. Inclusion criteria were: All published studies of intravenous immunoglobulin (IVIG) usage in the prophylaxis of infection in preterm and low birth weight infants from 1986 to present. Exclusion criteria: studies involving the use of IVIG in the active treatment of sepsis, studies involving neonates ≥ 37 weeks or ≥ 2500 g at birth.

Results

Table 1

Table 1

Study	Study type	Sample Size	Relative Risk [95% CI]	Results and Conclusions
Haque, et al. [8]	RCT	150	0.29 [0.11, 1.42]	Lower infection rate in group treated with IVIG. 16% → 4% infection. Suggests IVIG may protect neonates from sepsis.
Chirico, et al. [9]	RCT	133	0.25 [0.06, 1.11]	Lower infection rate in group treated with IVIG. 77% → 51% infection. 20% → 5% septicaemia. Supports IVIG being safe and effective in prophylaxis of neonatal sepsis
Stabile, et al. [10]	RCT	94	1.39 [0.33, 5.88]	No significant difference observed between treated and control groups
Clapp, et al. [4]	RCT	115	0.10 [0.01, 1.69]	No infant who received IVIG acquired nosocomial sepsis. Administration of sufficient IVIG to maintain target serum IgG levels throughout hospitalization may decrease the incidence of nosocomial sepsis in preterm infants.
Conway, et al. [11]	RCT	66	0.54 [0.26, 1.11]	Significant difference between experimental group and control group with regards infection (p = 0.01), less significant difference in those who developed culture-proven septicaemia (p = 0.09)
Ratriswadi, et al. [12]	RCT	102	0.38 [0.19, 0.79]	Suggests IVIG is effective in prophylaxis of sepsis, 250mg/kg just as effective as 500mg/kg dose. 38.2% → 14.7% infection
Baker, et al. [13]	RCT	588	0.8 [0.45, 1.39]	IVIG is well tolerated and reduced the incidence of infection in low-birth weight infants
Fanaroff, et al. [14]	RCT	2416	0.91 [0.77, 1.07]	Slight reduction in cases of sepsis. 17% → 16%. Not statistically significant. IVIG failed to reduce the rate of infection and sepsis in preterm infants.
Weisman, et al. [15]	RCT	753	1.16 [0.82, 1.64]	A single infusion of IVIG, 500 mg/kg, shortly after birth was not effective prophylaxis for late-onset infection in premature neonates
Lacy, et al. [16]	Meta-analysis	5245, 17 studies	-	After applying stricter inclusion criteria to lessen heterogeneity, reduction in infection rate changed from demonstrable to none.
Jensen, et al. [17]	Meta-analyses	4933, 12 studies	-	The addition of IVIG to standard therapies is of minimal but demonstrable benefit in the prophylaxis of sepsis when given to premature low birth weight neonates
Sandberg, et al. [18]	RCT	81	0.72 [0.30, 1.70]	No reduction in the rate of sepsis in the immune-deficient group who received prophylactic IVIG when compared to control noted. IVIG did not improve immune competence in neonates born with low serum IgG < 4 g/L
Hill H, [19]	Review Paper	-	-	IVIG should not be used to prevent nosocomial infections in premature infants.
Hemming V, [20]	Review Paper	-	-	While IVIG in the prophylaxis of infectious diseases in those with agammaglobulinaemia is effective, IVIG in the use of immunocompromised patients, including LBW preterm neonates, should be discouraged.
Ohlsson, et al. [6]	Cochrane systematic review	5000	-	3% reduction in sepsis rate. 4% reduction in nosocomial infection rate. No significant reduction in other co-morbidities or mortality. Encourages that further RCT's should not be conducted, and other avenues should be explored.
Goodarzi, et al. [21]	RCT	92	0.06 [0.004,0.99]	Prophylactic IVIG is effective in reducing nosocomial infections and duration of hospitalisation in preterm and LBW neonates but does not affect IVH, BPD, and NEC rates

Discussion

The effectiveness of IVIG as a prophylactic agent has been reported in many studies, both prospective and retrospective, ranging in population from 20 to 2416. Most of these studies were performed between the mid-'80s to late '90s.

The use of immunoglobulins for the prevention of sepsis followed Bruton's discovery in 1952 in which he reported the case of a young boy with agammaglobulinemia and recurrent streptococcal bacteraemia who subsequently had a reduced number of infections following administration of serum IgG. The study demonstrated the potential use of immunoglobulins for susceptible individuals with low serum IgG levels [22].

Haque, et al. and Chirico, et al. [8,9] conducted randomised control trials in Saudi Arabia and Italy respectively which suggested that intravenous IgG offered a protective benefit against infection and septicaemia in high-risk infants. However, neither study was blinded or placebo-controlled. Later trials by Stabile, et al. and Conway, et al. [10,11] offered less promise, concluding there was little difference in septicaemia rates between the treated and placebo groups.

Clapp, et al. [4] was one of the most influential early studies to explore this subject. This randomised control pilot study trialled 115 infants weighing < 2000 g. The IgG recipient group had a target serum level of 700 mg/dL. No infants who received IgG developed nosocomial sepsis. All nine infants who developed sepsis in the placebo group had an IgG concentration of < 400 mg/dL. This finding, that IgG below a certain threshold puts neonates are higher risk of sepsis, was monumental in instigating further studies into exploring the use of IgG for infection prevention.

Ambiguous results in these smaller study populations prompted the emergence of larger trials. Baker, et al. [13] performed the first large multicentre, randomised, double-blinded trial in which 400 mg/kg of IVIG was given to 287 infants on five occasions, with a control group of 297 subjects receiving placebo. Among the IVIG recipient group, the rate of infection was 32.4%, compared to 46.8% in the group receiving placebo. In those with identified infection in both groups, the length of hospital stay was lower in the group receiving IVIG prophylaxis. Baker, et al. [13] found that while no reduction in case-fatality rates among preterm neonates given IVIG was noted, a considerable benefit was associated with IVIG administration, infection risk and hospitalisation duration.

The Fanaroff, [14] study was a much larger multicentre trial enrolling 2416 preterm infants that accounted for between 42.7% and 61% of the statistical weighting in all meta-analyses and systematic reviews to date. When considering sepsis only, the phase 1 trial showed a rate of

sepsis of 11.6% in the immune globulin group and 16.4% in the control group. The study went from being double-blinded (in phase 1) to non-blinded (in phase 2) due to concerns over higher rates of Necrotising Enterocolitis (NEC) development in the group receiving IVIG prophylaxis. In phase 2, the rate of septicaemia became higher in the immune globulin group than in the control. With the introduction of potential bias, the change in pattern of outcome variables puts into question the validity of the study and consequently brings the validity of the larger reviews into question.

A post hoc analysis of the study revealed that while the immunoglobulin therapy appeared to have little effect on nosocomial infections caused by gram-negative species, there was a considerable reduction in infections caused by Group B Streptococcus (GBS). Furthermore, only one lot out of four IVIG preparations was shown to have a statistically significant reduction in the rate of nosocomial infection. Both of these findings may indicate variability across IVIG preparations and that the antibodies within certain preparations may or may not have an affinity for specific neonatal pathogens. This demonstrates the possibility that within the donor pool of a particular preparation, there could exist discrepancy regarding antibodies with the right antigenic affinity for GBS. If this is the case, it could offer a justification for the inconsistencies across studies, as well as support the future research of antigen-specific antibody preparations [14].

A further large multicentre trial was conducted by Weisman, et al. [15] who used a single immunoglobulin preparation of 500 mg/kg within the first twelve hours of birth. They noted that while this appeared to be a safe dose to give neonates to maintain higher levels of serum IgG, no significant difference was noted between the control population who received albumin and the treatment group. The authors suggested further studies examine antigen-specific immunoglobulin assays which would be more specific to the pathogens common in specific neonatal intensive care units.

In the first meta-analyses performed by Lacy and Ohlson, [16] it was concluded that routine administration of IVIG was not recommended for the prevention of infection in preterm infants. Although recognised variations across donor pools of IVIG preparations were noted as a limitation in this study.

Subsequently, a meta-analysis by Jenson and Pollock, [17] demonstrated that the use of IVIG in addition to standard therapy is of minimal but demonstrable benefit when administered prophylactically. As studies that confirmed sepsis by diagnosis through means other than true positive blood cultures were excluded by this meta-analysis, the more subtle benefits of IVIG may have been overlooked.

Jenson and Pollock [17] challenged the previously proposed notion that variations in IVIG preparations could lessen the validity of the prior study outcome. They performed a subclinical analysis of 6 studies that all used the same IVIG preparation, Sandoglobulin, and found no change in heterogeneity. This conclusion was consistent with the overall meta-analyses' findings [18]. However, it was recognised in a more up to date meta-analysis by Lacy and Ohllson, [6] that the necessary antibodies for combatting infection may yet still be absent from the IVIG preparation.

Sandberg, et al. [18] conducted a multicentre prospective randomised control trial which unlike previous studies on the topic excluded neonates with serum IgG levels > 4 g/L. Only 85 neonates of the anticipated sampled size of 400 neonates were included, as they were identified as having serum IgG levels of < 4 g/L taken within 24 hours of gestation. While the paper found no evidence that vulnerable neonates benefit from IVIG prophylaxis, the paper noted that the rate of infection was significantly lower in neonates born with a higher serum IgG. This speaks to the prognostic importance of IgG concentration at birth. Sandberg ultimately recommended alternative strategies that may improve the immature components of the neonatal immune system be explored.

Lacy and Ohlson, [6] combined data from 19 studies involving a total of 5000 infants. Of the 19 studies, only one study by Ratriswadi found a statistically significant reduction in sepsis. With all studies combined, results showed a statistically significant (p = 0.02) reduction in sepsis of 3%. Results for the secondary outcome; serious infection, also showed a statistically significant reduction in IVIG subjects of 4%. The quality of this meta-analysis was challenged by potential bias and substantial heterogeneity. Five studies were considered high quality, while bias could not be excluded for the remaining fourteen. Based on these findings, the authors concluded that such a small reduction does not warrant the use of IVIG and advised further RCT's in IVIG prophylaxis should not be considered.

A more recent small trial was performed in Iran by Goodarzi, et al. [21] more recently. The results of this single-blinded randomised control trial support the likelihood of IVIG conferring benefit to preterm low birth weight neonates. However, the reported results should be taken tentatively due to the limited number of patients as well as the potential introduction of bias with a single-blinded.

While the studies over the past 20-30 years have led to considerable ambiguity over the efficacy of prophylactic IVIG, the collective body of research illustrates a message that is quite clear. Whether a benefit from prophylactic IVIG does or does not exist, the degree of benefit found is so minimal that IVIG prophylactic administration cannot be justified for routine use. Even considering the limitations of the larger review studies, on evaluation of each individual study, the meta-analyses seem to offer a fair representation of IVIG efficacy.

The reason for the ineffectiveness of immunoglobulins in these infants remains unknown. However, researchers have suggested several factors; the presence of significant risk factors in these infants; concern over the efficacy of antibody

preparations for use against neonatal infection; and the immune immaturity beyond that of antibody deficiency all offer some insight.

The overall immaturity of the neonatal immune system extends beyond that of antibody deficiency. Stabile, et al. [10] highlighted that immunoglobulins only correct the immunological deficit in part. One of the main functions of IgG is opsonization. According to studies, opsonic activity in exogenous IgG recipients remains decreased [15]. In addition, several papers suggest that the humoral factors which work synchronously with antibodies, crucial for optimal function, are also impaired [14]. Despite this, studies have shown a direct correlation between increased maternal antibodies and decreased infectious episodes. Given the study results, this indicates a potential difference in immune coverage offered by maternal IgG and exogenous IgG. This is further highlighted by Hill, [19] who proposed that maternal immunoglobulins may contain specific antibodies to pathogens with which the mother and therefore her infant is more likely to be colonised.

Given the disappointing results of IgG immunotherapy, the use of antigenic-specific formulations may offer more promise. In 1998, a monoclonal antibody, Palivizumab, was licensed by the FDA for use in infants and young children with Respiratory Syncytial Virus (RSV) as it resulted in a substantial reduction in hospital stay, duration and infection severity. Developments like this may ensue for specific neonatal pathogens, but currently, further studies are needed [20].

At present, there appear to be a number of critical gaps in the knowledge informing these studies, particularly concerning the more complex interactions between neonatal defence mechanisms and bacterial virulence factors [16].

Recommendation

Further studies are needed to better our understanding of the neonatal immune response to sepsis. Without this understanding, the opportunities to discover therapies to treat and prevent these devastating infections remain limited.

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