Review Article

Intravenous Immunoglobulin in Neonates: Current Perspective

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Abstract

IVIG is being used off-label in newborns for sepsis prophylaxis, treatment of neonatal alloimmune diseases such as HDN & NAIT.Though earlier studies supported IVIG prophylaxis in neonatal sepsis prevention, latest INIS Trial showed that IVIG is not recommended to prevent neonatal sepsis. Use in treatment of sepsis remains controversial. Cochrane systematic review suggested a beneficial effect on mortality. Significant reduction in mortality occurred with addition of IgM-enriched IVIG. Nowadays IVIG is being increasingly used in Hemolytic Disorders mainly blood group incompatibility. It has been found to reduce multiple exchange transfusions, length of hospital stay & duration of phototherapy. Possible side effects include fever, allergic reactions, hypoglycaemia, hypotension, haemolysis, fluid overload & anaphylaxis. Pending FDA approval, prompt & judicious administration of IVIG with close monitoring for any adverse events is mandatory.

Key words: Intravenous Immunoglobulin, Hemorrhagic disease of newborn, sepsis prophylaxis.

Introduction

IVIG is concentrated, purified solution ofimmunoglobulins derived from pooled donor plasma. Inspite of approval for use in children, there are no FDA approval for newborns [1]. However it is being used off-label in newborns for sepsis prophylaxis particularly in LBW infants & treatment of neonatal alloimmune diseases such as HDN&NAIT. Recently IVIG has been used in parvovirus B19 infection, hemochromatosis & neonatal Kawasaki disease.

Mechanism of action: The proposed mechanism of action include.

1. Antibodyspecific immunity-Providing opsonic antibody against pathogens enhancing phagocytosis & neutrophil mediated killing of bacteria [2, 3].
2. Improving B cell function & complement system [4, 5, 6].
3. Blocking Fc receptor & thereby blocking binding of antibody to antigen [7].
4. Binding to fragment crystallizable receptors on phagocytes, NK cells & Reticulo-endothelial cells.
5. Neutralizing toxins, immunomodulating T cells & macrophages.
6. Down-regulation of inflammatory cytokines [4, 8].
7. Improving neutrophil chemiluminescence [2].
8. Improving Neutropenia byenhancing the release of stored neutrophils [9].

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Prophylaxis in sepsis: TransplacentalIgG transfer begins at 8-10 weeks of age & accelerates after 32 weeks gestation. So preterm infants have decreased immunoglobulin concentrations & also have an increased susceptibility for sepsis [10]. They respond to a harmful insult with an attenuated innate immune response. This protective response to prevent organ damage in utero becomes harmful after birth [11]. Moreover immunoglobulin levels decline further after birth.This relative IgG deficiency has upto 86-fold increased rate of sepsis in newborns with birth weight of 600-900 grams compared with those weighing more than 2,500 grams [11]. Earlier many studies [12, 13, 14] found that IVIG prophylaxis significantly reduced the number of infective episodes. Howeverin a systematic review of 19 trials involving >5000 preterm / LBW infants, prophylactic IVIG reduced the rate of late-onset infection by 3% with no significant reduction in mortality [15].Other studies found [16,17,18,19] found

no effect of IVIG in neonatal sepsis prevention. According to latest INIS Trial, IVIG is not recommended to prevent neonatal sepsis (grade A recommendation, level Ia evidence) [20].

Adjunctive therapy in sepsis: IVIG has been used for the treatment of neonatal sepsis since 1980's, but its usage remains controversial [15,21,22]. Three Cochrane systematic reviews, including nearly 6000 patients, suggested positive effects on mortality with use of IVIG in proven or suspected sepsis of preterm newborn [15,23]. Cochrane systematic review & meta-analysis of IVIG used for treating sepsis in neonates suggested a beneficial effect of IVIG on all cause mortality (RR 0.64) [24]. Other Studies have shown an increased mortality in septic neonates given antibiotics without IVIG, compared to thosegiven antibiotics plus IVIG [25, 26]. A systematic review of 7 trials of adjunctive therapy of IVIG involving 338 newborns of any gestational age that had suspected/ proven sepsis showed no difference in mortality [24].

IgM has the capacity to induce pronounced activation of complement system. IgM activates 100-400 fold more complement than IgG & is a more effective killer of bacteria. Opsonisation by IgM is also 1000-fold greater than IgG [27].

It is more potent against the septic process, possibly because of its size, which permits a more efficient inhibition of the lipopolysaccharide core on the bacterial surface during neonatal sepsis. Various systematic reviews on the use of polyclonal IgM-enriched IVIG in severe sepsis in neonates found significant reduction in mortality with addition of IgM-enriched IVIG [15, 28, 29, 30,31]. Two clinical trials [32,33] & a Metaanalysis [28] showed that patients with gram-negative sepsis had a significantly lower rate of mortality after IgM-enriched IVIG compared with control groups.However another study evaluating use of IgM-enriched Ig for the treatment of sepsis in 44 preterms showed that mortality in control group (37.5%) & immunotherapy group (30.0%) were not significantly different. A multicentric placebo controlled trial showed significant decrease in mortality in first 7 days, while survival at 56 days had not improved significantly [25].

Cochrane Database update showed that the use of IgM-enriched IVIG is still insufficient to support a conclusion ofbenefit on neonatal sepsis [24]. In 2011the INIS Study showed from a double-blind, randomized, placebo controlled trial in 3493 infants diagnosed with suspected or culture-proven sepsis that IVIG did not change the primary outcome of mortality or major disability at 2 years of age [20].

Hemorrhagicdisease of the newborn: Blood group incompatibility is reported to occur in 15%–25% of pregnancies [34]. Neonatal IVIGuseforhemolyticanemia was first reported in 1987 in the treatment oflateanemia due to rhesus E incompatibility [35]. It was then used in other forms of Hemolytic Disorders mainly blood group incompatibility [36, 37, 38,39]. Most studies have compared IVIG with the need for exchange transfusion and almost all have found a reduction (Grade A) [31, 36, 37, 38, 40, 41, 42]. There is also a significant reduction in the number requiring multiple exchange transfusions (RR 0.22), length of hospital stay (WMD −1.06) & duration of phototherapy (WMD −0.87). The NNT to prevent one exchange transfusion is very low at 2.7 [42]. AAP recommends IVIG as an adjunct therapy in the management on HDN [37]. AAP 2004 guidelines recommend administration of IVIG in isoimmune haemolytic disease if the TSB is risingat 8-17 micromol/L/hour despite intensive phototherapyor the TSB level is within 34–51 μmol/l (2–3 mg/dl) of the exchange level. IVIG also decreases the risk of neurological impairment as it decreases time in the high-risk zones on the Bhutaninomogram [36]. Multiple dose IVIG resulted in a greater percentage reduction in the need for exchange transfusion [43].

The NHS report suggests IVIG use in selected cases of HDN with worsening hyperbilirubinaemia (grade B recommendation, level III evidence) [44] whereas a meta-analysis of RCTs showed grade A, level 1a evidence [37,39]. However, no consistent effect of IVIg on duration of phototherapy has been observed [38]. A study reported considering IVIG in Zone 4 for preterm infants & Zone 5 for term infants [45].

ABO hemolytic disease: Useof IVIG in ABO hemolytic disease has been reported in a few studies [46, 47]. It reduces the need for exchange transfusion without producing immediate adverse effects in ABO hemolytic disease with positive direct Coomb's test.

Alloimmunethrombocytopenia: In the neonatal period, IVIG has been used for the treatment of alloimmunethrombocytopenia [48, 49]. It is recommended for NAIT if other treatments fail (grade C recommendation, level III evidence) & is effective in 75% of cases. High-dose IVIG (400 mg/kg day over 5

days) has been shown to be effective in infants with NAIT in few case reports [49, 50, 51].

Neonates of mothers with ITP: In newborns without evidence of ICH/ or other serious bleeding, treatment with IVIG may be appropriate if platelets are < 50 x 10^9/L. Newbornswithimaging evidence of ICH should be treated with IVIG & platelet transfusion.

Kawasaki disease: It is an acute, febrile, multisystemic inflammation of the blood vessels that strike predominately newborns& small children.IVIG has been reported to be of use neonatal Kawasaki disease [52].

Adverse effects: IVIG has been deemed safe & is mostly well tolerated [7, 47]. Possible side effects similar to blood transfusions occur like fever, allergic reactions, hypoglycaemia, hypotension, haemolysis, fluid overload & anaphylaxis (reported in IgA deficiency) [39]. Recently, an association with NEC has been described, but other factors in the development of NEC such as prematurity & prenatal risk factors could not be ruled out [36,53]. Use of high-dose IVIG for severe isoimmunehemolytic jaundice has been associated with a higher incidence of NEC [54]. Slow infusion (at least during 4 hours) reduces the effects of hyper viscosity [53]. There is a significant increase in number of RBC transfusions required for late anaemia in those who received IVIG (RR 8.0). Unlike Exchange Transfusion, the antibody is not being washed out with IVIG use. When the effect of IVIG has worn off, the Fc sites on the surface of reticuloendothelial cells become free to bind antibody sensitised neonatal erythrocytes, thus causing haemolysis.Rare but serious side effects such as transfusion transmitted diseases, hypersensitivity, thrombosis, pulmonary emboli, cytopenia& renal failure have been reported [30,54,55].

Conclusion

IVIG is being increasingly used in neonates for various conditions. Pending FDA approval, prompt & judicious administration of IVIG with close monitoring for any adverse events is mandatory.

Abbreviations

AAP American Academy of Pediatrics

FDA Food & Drug Administration

HDN Hemorrhagic Disease of the Newborn

ICH Intracranial Hemorrhage

IVIG Intravenous Immunoglobulin

LBW Low Birth Weight
NAIT Neonatal Alloimmune Thrombocytopenia

NEC Necrotising Enterocolitis

NK Natural Killer
NNT Number Needed to Treat
RBC Red Blood Cell
RCT Randomised Control Trials

RR Relative Risk
TSB Total Serum Bilirubin
US United States
WMD Weighted Mean Difference

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