Gammaglobulins in critical care

Gamaglobulinas em Terapia Intensiva

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ABSTRACT

The use of intravenous immunoglobulin (IVIG) is relatively infrequent in patients admitted to intensive care units (ICUs). However, "off-label" IVIG prescriptions for different conditions are highly prevalent. The aim of this paper is to review the existing evidence for the use of IVIG in patients admitted to ICUs, emphasizing non-infectious diseases and complications: hypogammaglobulinemia of the critically ill, hemophagocytic lymphohistiocytosis (HLH), Guillain-Barré syndrome (GBS), Kawasaki disease (KD), chylothorax, acute myocarditis, toxic shock syndrome (TSS), Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), and sepsis.

In conclusion, in critically ill patients, IVIG use is of benefit in KD, GBS, and TSS. It may benefit patients with fulminant acute myocarditis. The benefit is not proven in patients with HLH, chylothorax, and SJS/TEN.

Keywords: Immunoglobulin. Gammaglobulin. Critical Care. Intensive Care.

Introduction

Intravenous immunoglobulin (IVIG) is derived from great amounts of human serum, prepared for intravenous injection. Initially developed during the 1940's for intramuscular use, its use became more disseminated only after the availability of the intravenous preparation, by the end of the 20th century. Since it shows a variety of activities, IVIG has been investigated in the prophylaxis and treatment of a number of infectious and non-infectious diseases. Currently, the Food and Drug Administration (FDA) approves only six indications for the use of IVIG: primary deficiency of gammaglobulins, idiopathic thrombocytopenic purpura, Kawasaki disease (KD), HIV infection in children, chronic β-cell lymphocytic leukemia, and bone marrow transplant.[1]

However, many other "off-label" uses have been investigated and even recommended, including severe sepsis, septic shock, toxic shock syndrome (TSS), non-immune thrombocytopenia, prophylaxis of perioperative infections[1], Guillain-Barré syndrome (GBS), hemophagocytic lymphohistiocytosis (HLH), chylothorax, acute myocarditis, and Stevens-Johnson syndrome (SJS). A recently published review of IVIG use in 12 academic centers in the United States (US) showed that IVIG is used for more than 50 different conditions. Fifty-two percent of them were considered "off-label".[2] In a Canadian study, IVIG use in patients admitted to intensive care units (ICUs) was relatively

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infrequent: from 145 prescriptions, 19% were considered adequate, while 74% were considered "off-label," and 7% were considered inadequate.[1] In that study, the main indications for IVIG use were GBS, toxic epidermal necrolysis (TEN), and necrotizing fasciitis.

Given the controversy regarding the use of IVIG, especially in critically ill patients, the objective of this article is to review the usefulness of IVIG in critically ill patients, with emphasis on non-infectious diseases and complications.

Hypogammaglobulinemia of critically ill patients

During a critical illness, adult and pediatric patients can exhibit low plasma concentrations of immunoglobulins. In children admitted to the ICU, the incidence of hypogammaglobulinemia can reach 70%.[3,4] The meaning of this phenomenon is not clear. It is possible that it is a normal part of acute response to stress, just like alterations in cortisol, insulin, and endogenous catecholamines, but it is also possible that the phenomenon is associated with a transient immunodeficiency with impairment of the host defenses against pathogenic microorganisms.[3]

To date, there is no evidence to support routine immunoglobulin supplementation in critically ill patients. However, patients with severe infections and documented hypogammaglobulinemia may experience benefit.[3]

Hemophagocytic Lymphohistiocytosis (HLH)

HLH is a severe disease that can occur as a familial type, or as a secondary reaction to infectious, rheumatologic, or malignant diseases.[5] When HLH is secondary to rheumatologic diseases, it can also be named macrophage activation syndrome (MAS). The initial diagnosis is clinical, based on the presence of fever, splenomegaly, cytopenia, elevated ferritin, elevated triglycerides, and lowered fibrinogen. There can also be impairment of natural killer cell function and elevated soluble CD25.[5] The diagnosis is confirmed by the presence of hemophagocytosis in bone marrow aspirates.[6]

The majority of patients require intensive care during the episodes. However, the best therapeutic regimen is not established. It can include corticosteroids alone, IVIG alone, or different combinations of corticosteroids, IVIG, etoposide, and cyclosporine. The efficacy of IVIG in this setting is not still well established.[5]

In a study of 38 children with HLH/MAS in Canada, the use of corticosteroids and/or IVIG as first line treatments was considered sufficient.[5] Parekh et al published a series of 3 children with HLH where all received IVIG, and they reported disease remission after 3–7 weeks.[7] Lin et al studied 8 children with MAS and concluded that IVIG use (1 g/kg/day) was efficient in controlling the disease in 33% of cases, as well as cyclosporine and corticosteroids in the other cases.[8]

Since studies addressing IVIG use in HLH/MAS are scarce and controversial, the efficacy of IVIG in these conditions is still not established.[9-13]

Guillain-Barré Syndrome (GBS)

GBS is currently the most common cause of flacid acute paralysis after the reduction of the incidence of poliomyelitis. The syndrome usually follows an acute bacterial or viral infection. The most common agent is *Campylobacter jejuni*, but the disease can also follow vaccination against measles, tetanus, poliomyelitis, *Meningococcus*, rubella, influenza and hepatitis B. It is characterized by ascending polyneuropathy, frequently involving motor nerves and, less often, sensorial and autonomic nerves. It starts with progressively ascending symmetric muscle weakness that can involve the respiratory muscles and lead to respiratory failure with need for mechanical ventilation.[14]

The use of IVIG patients with GBS admitted to ICUs is discussed elsewhere in this issue. In summary, IVIG is considered as effective as plasma exchange in hastening symptoms of GBS if started within two weeks from disease onset.[15]

Kawasaki Disease (KD)

KD is an acute, self-limited vasculitis occurring mainly in children of all ages.[16] The disease can lead to coronary artery aneurisms, being the main cause of acquired heart disease in children from developed countries. The fist-line treatment includes aspirin and IVIG[17], but some patients may not respond. Besides, the first-line treatment may be delayed due to incorrect diagnosis of septic shock or TSS.[16] In a large cohort of 423 children with KD, those who needed admission to an ICU (3.3%) have had longer delays in administration of IVIG, and higher proportion of IVIG resistance. These patients needed a second dose of IVIG or other immunosuppressant therapy.[16]

In 1984, Japanese researchers published a randomized clinical trial on two different treatments for

KD: aspirin (n=45) versus IVIG (n=40). Patients treated with IVIG had lower incidence of coronary aneurisms after 29 days (15 vs. 42%).[18] Two years later, Newburger et al published another study on 79 children with KD, and concluded that a high-dose of IVIG (400 mg/kg/day for 4 days) was safe and effective in decreasing the incidence of coronary abnormalities if administered early in disease course.[19]

Recently, a retrospective study on 359 children with KD who did not respond to the initial IVIG dose showed that rescue therapy with IVIG plus prednisolone was more effective than IVIG or prednisone alone in controlling the disease.[17] This year, Park et al published a study on 309 children with KD, of whom only 30 (7.9%) did not respond to an initial IVIG dose. Patients who did not respond to IVIG had longer hospital stay and higher incidence of coronary lesions. Two risk factors for first-dose IVIG resistance were identified: ALT ≥ 84 IU/L and total bilirubin ≥ 0.9 mg/dL.[20]

Therefore, IVIG is effective in decreasing the incidence of coronary disease after KD, and can also be used as a rescue therapy after first-dose failure, associated or not to corticosteroids.

Chylothorax

Chylothorax is a relatively rare complication, occurring more commonly after pediatric heart surgery. Its estimated incidence is between 1 and 5%.[21] This complication can lead to higher morbidity and longer ICU and hospital stay. The lymphocyte depletion and gammaglobulin loss in the lymph can lead to secondary immunodeficiency. Since IVIG use is well established in the treatment of primary immunodeficiencies, it could be useful in this setting. However, the guidelines for chylothorax management do not emphasize the need of immunoglobulin replacement.[22]

McBride et al reported 2 cases of chylothorax following heart surgery in children that resulted in hypogammaglobulinemia. In this study, serum level of gammaglobulins increased after IVIG infusion.[22] In another study, on a cohort of 37 children with chylothorax after heart surgery, those with greater lymph losses exhibited lower serum levels of gammaglobulins. However, IVIG use did not lowered the incidence of infections.[21]

Therefore, IVIG use in patients with chylothorax following heart surgery can increase serum levels of gammaglobulins, especially when they are low, but the benefit is not established yet.

Acute Myocarditis

Acute myocarditis is defined as an acute inflammation within the myocardium caused by a non-specific viral infection.[23] Its severity can vary from subclinical dysfunction up to heart failure and cardiogenic shock.

Treatment includes mechanical ventilator support, inotropes like milrinone, dobutamine and levosimendan, and, in severe cases, mechanical circulatory support. The most used modalities for circulatory support are extracorporeal membrane oxygenation (ECMO) and ventricular assistance devices (VAD). In cases where the myocardium do not recover, heart transplantation might be necessary.[24]

In the pediatric population, some studies have reported success after immunomodulatory treatments with IVIG and corticosteroids, alone or in combination.[23] In animal models of myocarditis, IVIG use showed encouraging results, but in humans the results were disappointing.[24] In France, in a series of 11 cases of children with acute myocarditis, all received corticosteroids, and seven received IVIG (2 g/kg in 24 hours). In this series, only one death (9%) was recorded.[23] In a multicenter trial with 216 children with acute myocarditis, 49.1% received IVIG as part of their treatment. However, IVIG did not alter mortality, not even in the subgroup of more severe patients.[25]

Therefore, routine IVIG use in acute myocarditis is not recommended, although some authors still advocate it in patients with fulminant myocarditis.[24]

Toxic Shock Syndrome (TSS)

TSS is an invasive infection caused by group-A β-hemolytic *Streptococci*.[26] Mortality is extremely high (up to 80%) despite antibiotic therapy.[26] It is characterized by hypotension and multiple organ failure early in disease course. There is evidence that lack of humoral immunity protecting against bacterial superantigens might be involved in the genesis of the disease. This fact led many authors to propose IVIG use for treatment of TSS, because of the possibility of superantigens neutralization and enhanced opsonization.[26]

In 1999, Kaul et al published a series of 21 cases of TSS treated with IVIG (2 g/kg/day) compared to historic controls. Patients that received IVIG have had a higher survival rate (67 vs. 34%, p=0.02).[27] Later, a randomized multicenter trial on 21 adult patients with TSS (10 received IVIG) showed a 3.6-fold reduction in mortality and a significant reduction on the incidence

of multiple organ failure in patients receiving IVIG.[26] In a larger randomized multicenter trial of 192 children with TSS, 84 (44%) received IVIG as part of their treatment regimen. For these patients, total hospital cost was significantly higher, and outcomes were the same.[28]

Therefore, IVIG use is associated with decreased mortality in adults with TSS. In children, the benefit is still unproven.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN are severe cutaneous reactions, usually to drugs, associated with disseminated epidermal destruction.[29] Both diseases are closely related: SJS is a self-limited form characterized by erosions in mucous membranes and blisters in less than 10% of body surface area, while TEN resembles severe burns due to the confluence of erosions and blisters in more than 30% of body surface area. Therefore, there are cases with superposition of the two definitions, depending on the extension of skin lesions.[29] It is a rare condition (1.5-–2 cases per million inhabitants per year), but with high mortality (20–25%).[30]

No treatment has been proven as beneficial for these diseases to date. Many authors advocate the use of corticosteroids and immunosuppressant drugs. Laboratory data suggest that IVIG might be useful because it can prevent Fas-ligand protein from binding to Fas receptor, which is augmented in the disease.[31] However, to date, no prospective study confirmed the IVIG utility in patients with SJS/TEN.[32] Most benefits have been shown in retrospective studies.[30]

In a study of 12 patients with TEN in Europe and United States, treatment with IVIG (1 g/kg/day for 3 days) resulted in faster resolution of epidermal detachment and 88% survival.[33] In Italy, 10 patients with TEN received smaller doses of IVIG (400 mg/kg/day for 5 days) and had a lower-than-predicted mortality (10 vs. 35%).[34] Metry et al showed that the same benefit extends to pediatric patients.[35] In that study, involving 28 children with SJS/TEN, appearance of new blisters was halted 24–48 hours after IVIG infusion. In France, in a study of 34 adults with SJS/TEN, all received IVIG (2 g/kg), and the observed mortality (32%) was superior to the mortality predicted by severity scores (24%), thus not supporting IVIG use for the treatment of SJS/TEN in adults.[29] Also in children, Morici et al compared the outcomes of patients with SJS who received (n=7) or not (n=5) IVIG (1.5-–2 g/kg), and observed that those receiving IVIG had shorter fever duration and shorter hospital stay.[36]

In the United States, another study compared patients with TEN who received (n=24) or not (n=21) IVIG, and showed that mortality was higher in patients receiving IVIG (41.5 vs. 28.6%, p=NS). In this study, patients receiving IVIG also had longer hospital stay.[32] In 2006, another retrospective study showed that IVIG use (2.8 g/kg/day) in 23 patients with TEN resulted in lower mortality (26%) compared to 8 patients who did not receive IVIG (75%).[30]

The larger retrospective study on IVIG use in SJS/TEN was published in 2008 (EuroSCAR) and included 379 patients. IVIG administration (1.9 g/kg) did not result in any benefit compared to support therapy.[37] The study used smaller-than-recommended doses of IVIG, and the group receiving IVIG had larger body surface involvement. The study by Yang et al, in 2009, on 65 patients (20 receiving IVIG) showed lower-than-predicted mortality on patients receiving IVIG, although differences were not statistically significant.[38]

More recently, a study compared clinical and treatment characteristics of children with SJS/TEN admitted to two different hospitals, one American and one Canadian, and showed that therapeutic regimens varied broadly between the two hospitals, but the outcomes were similar. IVIG use was higher in the American hospital (65 vs. 23%).[39]

Although most studies favor IVIG use in patients with SJS/TEN, some do not support the benefit. Many of these studies used IVIG doses below the recommended. Moreover, IVIG was administered too late in the disease course. Therefore, there is a need for controlled studies with adequate doses and timing of IVIG, so the benefits can be proven. Nevertheless, the benefits may not only involve reductions in mortality but also on halting disease progression.[30]

Sepsis

Controling the hyper-inflammation is one of the strategies used in the treatment of severe sepsis and septic shock. For this aim, it is very unlikely that the patient arrives in the emergency room early enough to control the hyper-inflammation with only one drug. Thus it seems that a combination of drugs may be more efficient.[40] Data extrapolated from pre-clinical studies suggest that IVIG administration may ameliorate bacterial elimination, inhibit nuclear factor *kappa*-B (NF-κB) activation, block inflammatory mediators, attenuate lymphocyte apoptosis, and have anti-inflam-

matory effects. However, it is still necessary to better characterize changes in blood levels of immunoglobulins that accompany sepsis, as well as the underlying mechanisms and the likelihood of benefits following IVIG administration.

Currently, the 2012 Guidelines of the Surviving Sepsis Campaign suggests "not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B)".[41] There are no recommendations for children.

Conclusion

In conclusion, in critically ill patients, IVIG use is of benefit in Kawasaki disease, Guillain-Barré syndrome and toxic shock syndrome. It may offer benefit to patients with fulminant acute myocarditis. The benefit is not proven in patients with hemophagocytic lymphohistiocytosis, chylothorax, and Stevens-Johnson syndrome/toxic epidermal necrolysis.

RESUMO

O uso de imunoglobulina intravenosa (IVIG) é relativamente infrequente em pacientes internados em unidades de terapia intensiva (UTIs). Entretanto, prescrições "off-label" de IVIG para diferentes patologias são altamente prevalentes. O objetivo deste artigo é revisar as evidências existentes para o uso de IVIG em pacientes internados em UTIs, enfatizando as doenças e complicações não infecciosas: hipogamaglobulinemia do paciente crítico, linfo-histiocitose hemofagocítica (HLH), síndrome de Guillain-Barré (GBS), doença de Kawasaki (KD), quilotórax, miocardite aguda, síndrome do choque tóxico (TSS), síndrome de Stevens-Johnson (SJS)/necrólise epidérmica tóxica (TEN), e sepse.
Em conclusão, em pacientes criticamente enfermos, o uso de IVIG é benéfico em KD, GBS e TSS. IVIG pode ser benéfica em pacientes com miocardite aguda fulminante. O benefício não foi comprovado em pacientes com HLH, quilotórax e SJS/TEN.

Palavras-chave: Imunoglobulina. Gamaglobulina. Terapia Intensiva. Cuidados Intensivos.

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