Original Investigation / *Özgün Araştırma*

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Clinical Indications of Intravenous Immunoglobulin Use in Pediatric Infectious Diseases Clinic

Çocuk Enfeksiyon Hastalıkları Kliniğinde İntravenöz İmmünoglobülin Kullanımının Klinik Endikasyonları

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Abstract

Objective: Intravenous immunoglobulin (IVIG) is a human polyclonal IgG preparation developed for the treatment of patients with primary immunodeficiency (PID). Because of the anti-inflammatory and immunomodulatory effects of IVIG, beyond PID now IVIG is widely used in autoimmune and inflammatory diseases. The aim of this study was to determine the demographic characteristics of patients treated with IVIG treatment in the pediatric infectious diseases clinic, and to evaluate the indications, side effects and treatment outcomes of IVIG treatment.

Material and Methods: Between October 2010 and May 2015, patients of 0-18 years who received IVIG treatment in pediatric infectious disease clinics were included in the study. The patient medical records were retrospectively reviewed. Demographic characteristics of patients, diagnoses, IVIG treatment protocols, treatment outcomes, side effects due to IVIG treatment were recorded. Side effects were recorded as rapid side effects, delayed side effects, and late reactions.

Results: A total of 279 patients were included in the study. Of the patients, 110 (39.7%) were female and 167 (60.3%) were male. According to treatment indications, 230 (83%) patients were in the group of immunologically mediated diseases, 22 (79.4%) were in the infectious disease group and 25 (9%) patients were primer immunodeficiency group. Among the rapid side effects, infusion site pain was observed in 34 patients (12.2%), redness in 14 patients (5%), and headache in 24 patients (8.6%). Delayed side effects were nausea and vomiting in 12 patients (4.3%), acute renal failure in one patient, and hyponatremia in 16 patients (5.7%). Late reactions were not observed in any of the patients.

Conclusion: Although the precise indications for the use of intravenous immunoglobulins are limited, taking into consideration the studies

Özet

Giriş: İntravenöz immünoglobulin (İVİG) primer immünyetmezlikli (PİY) hastaların tedavisi için geliştirilmiş insan poliklonal IgG preparatıdır. Günümüzde İVİG'in antiinflamatuvar ve immünomodülatör etkisi nedeniyle, PİY hastaların dışında otoimmün ve inflamatuvar hastalıklarda yaygın şekilde kullanılmaya başlandı. Bu çalışmada, Çocuk Enfeksiyon Hastalıkları Kliniği'nde İVİG tedavisi uygulanan hastaların demografik özelliklerinin belirlenmesi, İVİG endikasyonlarının, tedavi sonuçlarının ve İVİG tedavisine bağlı görülen yan etkilerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Ekim 2010-Mayıs 2015 tarihleri arasında Çocuk Enfeksiyon Hastalıkları Kliniği'nde İVİG tedavisi uygulanan 0-18 yaş arası hastalar çalışmaya dahil edildi. Hastaların dosyaları ve bilgisayar kayıtları retrospektif olarak incelendi. Hastaların demografik özellikleri, tanıları, İVİG tedavi protokolleri, tedavi sonuçları, İVİG tedavisine bağlı gelişen yan etkiler kaydedildi. Yan etkiler hızlı yan etkiler, gecikmiş yan etkiler, geç reaksiyonlar olarak kaydedildi.

Bulgular: Çalışmaya 279 hasta alındı. Hastaların 110 (%39.7)' u kız, 167 (%60.3)'si erkekti. Tedavi endikasyonuna göre immün aracılı hastalıklar grubunda olanlar 230 (%83) hasta, enfeksiyon hastalıkları grubundakiler 22 (%79.4), primer immünyetmezliği olanlar ise 25 (%9) hasta idi. Hızlı yan etkiler arasında infüzyon yerinde ağrı 34 hastada (%12.2), kızarıklık 14 (%5) hastada ve başağrısı 24 (%8.6) hastada gözlendi. Gecikmiş yan etkiler bulantı kusma 12 (%4.3) hastada, akut böbrek yetmezliği bir hastada, hiponatremi 16 (%5.7) hastada gözlendi. Geç reaksiyonlar hastaların hiçbirinde gözlenmedi.

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conducted, it has been shown to be beneficial in many clinical trials. Randomized controlled studies should be conducted to determine the effectiveness of IVIG in such diseases.

Keywords: Intravenous immunoglobulin, child

Sonuç: İVİG kullanımının kesin endikasyonları sınırlı olmakla beraber, yapılan çalışmaların ışığında klinikte bir çok hastalıkta yarar sağladığı gösterilmiştir. Bu hastalıklarda İVİG etkinliğini kesin olarak gösterebilmek için randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İntravenöz immünglobülün, çocuk

Introduction

Intravenous immunoglobulin (IVIG) is the most commonly used plasma product worldwide. IVIG is a human polyclonal IgG preparation obtained by pooling of plasma samples obtained from a high number of healthy donors. The activity of IVIG cannot be easily explained by a single mechanism. It shows activity by altering expression and functions of Fc receptors, by inhibiting inflammatory cytokines and stimulating production of anti-inflammatory cytokines, neutralizing activated complement complexes and the autoantibodies, stimulating the dendritic cells as well as T and B cells and by inducing changes in differentiation and functioning of these cell types (1-3).

Intravenous immunoglobulin was approved in 1981 by United States of America Food and Drug Administration (FDA) for the first time and was initially used as a replacement therapy in patients with immunodeficiency progressing with hypogammaglobulinemia. Table 1 lists the current FDA-approved indications (4). Apart from these diseases, currently, IVIG is commonly used for the treatment of acute, chronic or recurrent immune-mediated diseases, for autoantibody or T cell-mediated autoimmune diseases and for inflammatory diseases resulting from cytokine release imbalance. In 2017, the American Allergy, Asthma and Immunology Academy (AAAAI) study group reviewed several diseases that can potentially benefit from IVIG treatment and published an evidence-based, updated guideline on the use of IVIG therapy (3). The aim of the present study was to determine the demographic characteristics of patients treated with IVIG in pediatric infectious diseases clinics and to evaluate indications, treatment outcomes and side effects of IVIG treatment.

Table 1. FDA-approved indications for IVIG treatment (2017)

Replacement therapy
Primary humoral immunodeficiencies
B-cell chronic lymphocytic leukemia *
Immunomodulatory activity
ITP
Kawasaki disease
Chronic inflammatory demyelinating polyneuropathy
Multifocal motor neuropathy
* Hypogammaglobulinemia and/or associated with recurrent bacterial infections. FDA: Food and Drug Administration, ITP: Immune thrombocytopenic purpura.

Materials and Methods

Patients aged between 0-18 years, who received IVIG therapy at Dr. Sami Ulus Gynecology, Obstetrics, Pediatric Health and Diseases Training and Research Hospital Pediatric Infectious Diseases Clinics between October 2010-May 2015, were included in this study. As patients aged between 0-30 days were followed by neonatal care services, patients in the neonatal age group were excluded from the study. All patients received inpatient IVIG therapy. Medical files and electronic medical records of the patients were retrospectively reviewed. Demographic characteristics of patients, diagnoses, IVIG treatment protocols, treatment outcomes, and side effects associated with IVIG treatment were recorded. IVIG treatment was given in three different protocols. In the group with immune-mediated diseases, patients with Kawasaki disease were given a dose of 2 g/kg in 12 hours, patients in neurological and hematological diseases group were given doses of 400 mg/kg for five days or 1 g/kg for two days, and patients in infectious diseases group were given IVIG dose of 1 g/kg for two days. All patients were given paracetamol and avil before the IVIG treatment to reduce side effects. Side effects occurring within the first six hours following IVIG infusion were classified as fast-onset side effects, those developing after six hours and until one week of therapy were considered delayed side effects, and those developing weeks or months after IVIG use were considered late-term reactions. Medical indications for IVIG use were individually evaluated for each patient. Patients were classified into three groups based on treatment indications: those with immune-mediated diseases, primary immunodeficiency disorders and infectious diseases. According to the potential benefits defined by AAAAI, clinical use of IVIG was evaluated in four groups as definitely beneficial, possibly beneficial, potentially beneficial and no expected benefits.

Statistical analyses were performed using the SPSS program (15.0 version, Chicago, SPSS Inc.). Quantitative data were presented as mean ± standard deviation, and categorical data

were shown in frequencies (n) and percentages (%). Quantitative data were analyzed by Student's t-test if they were normally distributed and Mann-Whitney U test was used for non-normally distributed quantitative data. Categorical data were analyzed by Chi-Square test. P values lower than 0.05 were considered statistically significant.

Results

A total of 279 patients were included in the study and Table 2 presents their demographic characteristics. Of all the patients, 112 (39.7%) were female and 167 (60.3%) were male. The median age of the female and male patients was 38.5 months (minimum 2-204 months, IQR: 58) and 42 months (minimum 2-330 months, IQR: 54), respectively.

Table 2. Demographic characteristics of the patients

	Number (percentage)
Total number of patients	277 (100)
Gender	
Female	112 (40.2)
Male	167 (59.8)
Age	Median (minimum-maximum, IQR)
Female	38.5 ay (2 months-204 months, IQR: 58)
Male	42 months (2 months -330 months, IQR: 54)
IQR: Interquartile range.	

Based on treatment indications, immune-mediated disease group included 230 (83%) patients and formed the majority of patients receiving IVIG therapy. There were 22 (79.4%) and 25 (9%) patients in infectious diseases and primary immunodeficiency diseases groups, respectively. Table 3 shows the indications for IVIG therapy. In the immune-mediated diseases group, 40 (14.4%) patients had hematological diseases, 15 (5.4%) had neurological diseases, 160 (57.7%) patients had rheumatologic diseases and 15 (5.4%) patients had dermatological diseases. Of the patients receiving IVIG therapy due to diagnosis of an infectious disease, 11 (4%) had toxic shock syndrome, 7 (2.5%) had invasive group A streptococcus infection and 4 received prophylactic treatment following exposure to measles. IVIG treatment was given to 85 patients for an indication other than those approved by FDA.

Among the fast-onset side effects, infusion site pain and redness were observed in 34 (12.2%) and 14 patients (5%), respectively, while 24 patients (8.6%) experienced headache. Delayed side effects were nausea and vomiting in 12 patients (4.3%), acute renal failure in one patient, and hyponatremia in 16 patients (5.7%). Late-term reactions were not observed in any patient. As a majority of the patients were admitted to infectious diseases clinics with complaint of fever, fever was not

Table 3. Indications of patients given IVIG therapy

Immune-mediated diseases	**Number of patients (percentage)**
Hematological diseases	
ITP	9 (3.22)
Autoimmune hemolytic anemia	2 (0.72)
Hemophagocytic lymphohistiocytosis	28 (10)
Autoimmune lymphoproliferative syndrome	1 (0.36)
Neurological diseases	
Autoimmune encephalitis	7 (2.5)
Limbic encephalitis	3 (1.07)
Guillain Barre Syndrome	4 (1.43)
Acute disseminated encephalomyelitis	2 (0.72)
Transverse myelitis	1 (0.36)
Rheumatologic diseases	
Kawasaki disease	160 (57.3)
Dermatologic diseases	
Steven-Johnson syndrome/Toxic epidermal necrolysis	13 (4.65)
DRESS	2 (0.72)
Primary immunodeficiencies	25 (8.96)
Infectious diseases	
Toxic shock syndrome	11 (3.94)
Invasive group A streptococci infection	7 (2.5)
Prophylaxis after measles exposure	4 (1.43)
ITP: Immune thrombocytopenic purpura, DRESS: Drug Rash with Eosinophilia and Systemic Symptoms.	

considered as a side effect as it was not possible to differentiate whether fever was associated with the underlying disease or the IVIG treatment.

Discussion

While IVIG is primarily used in patients with immunodeficiency, only 9 percent of the patients in this study received IVIG infusion due to a PID syndrome. We believe that this rate was low because IVIG infusions to patients with PID are given in pediatric emergency services or in general pediatric services of our hospital, and these patients are admitted to infectious diseases clinics only if they have a concomitant infection.

Owing to its activity to regulate immune system, high-dose IVIG is used for the treatment of immune-mediated diseases. In the present study, apart from its use as a replacement therapy, over the last decade, we have focused on the increasing use of IVIG as an immune regulator.

Previous studies have indicated that IVIG can provide potential benefits when used for several other immune-mediated diseases (autoimmune and inflammatory), other than its FDA-approved indications (3). Therefore, over the years, IVIG use has become increasingly common. Studies have reported that FDA-approved indications account for 35-60 percent of total IVIG use (5). In the present study, the rate of IVIG use in FDA-approved indications was 70 percent, higher than those previously reported.

While the majority of patients with immune thrombocytopenic purpura (ITP) recover spontaneously, patients with bleeding problems and chronic disease still require treatment. Available treatment options for these patients include systemic corticosteroids, Anti-D IgG, IVIG, plasmapheresis, rituximab and/or combinations of these therapies (6,7). In addition to modulating immune system by blocking Fc receptors, IVIG also prevents degradation of thrombocytes by inhibiting binding of thrombocyte and anti-thrombocyte antibody complexes to phagocytic cells. In multi-central, randomized, controlled trials comparing high-dose IVIG with systemic corticosteroid therapy, IVIG treatment was shown to provide better clinical recovery and represent an important and beneficial treatment option in patients with severe ITP (3,6,7). Several case series demonstrated benefits of IVIG use in patients with autoimmune hemolytic anemia (8). In the present study, nine patients were given IVIG due to a diagnosis of ITP and two patients were given IVIG for treatment of autoimmune hemolytic anemia.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening, serious disease that can be hereditary or develop secondary to viral, bacterial, protozoal, fungal or parasitic infections, and malignancies or collagen tissue disorders. As the treatment of HLH was not investigated in any randomized controlled trial so far, available information on the treatment of HLH obtained from case series and case reports (9). High-dose IVIG can provide benefits in early period of the disease, particularly when used in combination with other therapies, but randomized controlled trials are required to clearly demonstrate these benefits. Previously, 10 patients who developed HLH secondary to brucellosis (8), leishmaniasis (1 patient), Epstein-Barr Virus (2 patients), ascariasis (1 patient) and salmonellosis (1 patient), and collagen tissue disease (5 patients), without an identified cause, were given IVIG therapy. None of these patients died.

IVIG is also commonly used for the treatment of pediatric neurological diseases. While there is no consensus on its use for treatment and potential benefits, a review of 65 studies has demonstrated that IVIG treatment shortened the duration of recovery in Guillain-Barre syndrome and was as effective as plasmapheresis, in addition to facilitating recovery in ADEM treatment. The same review also showed that early IVIG therapy can improve prognosis in autoimmune encephalitis. IVIG is a beneficial treatment option in select neurological disorders, such as those noted in our patient group (10).

Kawasaki disease is an acute, febrile childhood vasculitis that principally affects coronary arteries. IVIG treatment prevents cardiac complications particularly when used within the first 10 days after disease onset (11). As patients with Kawasaki disease are mostly referred with prolonged fever, they were admitted to pediatric infectious diseases clinics. This patient group accounted for the majority (57.7%) of patients receiving IVIG therapy.

Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis are rare diseases, but they are associated with high mortality rates. While prospective and retrospective multi-central studies showed that early administration of high-dose IVIG was helpful in terms of preventing disease progression and decreasing the rate of mortality, a meta-analysis of 17 studies did not demonstrate any statistically significant reduction in mortality (12). There is no consensus on the use of IVIG for treatment of these diseases, while the AAAI report suggested potential benefits of IVIG therapy in this disease group (3). One of 13 patients who were given IVIG therapy developed visual loss due to corneal involvement despite IVIG therapy. None of the patients died due to SJS.

Despite improvements in antimicrobial treatment options, there are still several infectious diseases that are difficult to treat or incurable at all. Therefore, although absolute benefits are equivocal, IVIG therapy is also used as support treatment in some infectious diseases and for prophylaxis of some others. In the present study, 22 patients were given IVIG therapy due to the diagnosis of an infectious disease. In a large-scale study including 3493 infants who were given antibiotherapy

for sepsis, the rates of 2-year mortality and morbidity were not found to be significantly different between patients receiving immunoglobulin and placebo (13). None of the patients were given IVIG due to sepsis. Invasive infections caused by group A Streptococcus (GAS) include sepsis, bacterial pneumonia, necrotizing fasciitis (NF) and streptococcal toxic shock syndrome (STSS), all of which are associated with high mortality rates. Due to its superantigen neutralizing antibody component, IVIG is considered to be effective on toxic shock. A case control study evaluating the use of IVIG for treatment of toxic shock syndrome reported reduced rates of mortality with IVIG therapy (14). In a study including 192 pediatric patients diagnosed with toxic shock syndrome, 84 patients were given IVIG treatment and no significant differences were noted with IVIG in terms of mortality, duration of hospital stay or other clinical variables (15). In the present study, IVIG therapy was given to 11 patients for the diagnosis of toxic shock and to seven patients for invasive GAS infection. All of those patients were discharged on recovery.

IVIG is generally considered as a safe therapy. Almost 5-10 percent of treated patients develop side effects (16). Side effects are usually related to the speed of administration, and a majority of them resolve spontaneously. As the frequency of side effects is lower among patients given premedication before IVIG therapy, in this study IVIG treatment was initiated after premedication and given through slow-infusion. In total, 9.3 percent of all the patients developed at least one side effect. The side effects were classified as fast-onset, delayed and late-term side effects. Infusion site pain and redness occurred in eight (2.9%) and four (1.4%) patients, respectively, while five (1.8%) patients experienced headaches. Infusion was temporarily terminated until symptoms regressed and continued at a lower rate once all the symptoms had disappeared. Delayed side effects were vomiting and hyponatremia, observed in four (1.4%) and four (1.4%) patients, respectively. Acute renal failure develops as a result of tubular damage caused by solid load of sucrose used in IVIG preparations. Close monitoring of renal functions is recommended in patients under risk of developing renal failure. In this study, one patient developed acute renal failure after IVIG treatment. Renal functions of that patient normalized after intravenous hydration. IVIG rarely may result in arterial or venous thrombosis, pulmonary embolism, myocardial infarction, stroke or obstruction of a retinal artery or vein (16). These thromboembolic events occur in patients under high risk of thrombosis, and they are associated with increased plasma viscosity or elevated levels of anticardiolipin antibodies. None of the patients in this study developed a thromboembolic event. The transmission of viruses such as hepatitis B virus (HBV), Human Immunodeficiency Virus (HIV), and hepatitis C virus (HCV) have been reported weeks to months after IVIG use. These are known as late-term reactions. None of the patients in this study experienced a late-term reaction.

In conclusion, IVIG is used as a replacement therapy in immunodeficiency disorders and as an immune modulator agent in autoimmune/systemic diseases. While precise indications of intravenous immunoglobulin are limited, previous studies have demonstrated the potential benefits of IVIGs in several diseases in clinical practice. Bearing in mind that IVIG is an expensive treatment associated with side effects, each patient should be individually evaluated and treatment decisions should be given by taking into account treatment indications, potential risks, patient-specific underlying risk factors and concomitant diseases.

Ethics Committe Approval: Ethics committee approval was not received due to the retrospective nature of this study.

Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

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