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Original Article

Assessment of Intravenous Immunoglobulin Indications in Pediatric Intensive Care

Çocuk Yoğun Bakımda İntravenöz İmmünoglobulin Endikasyonlarının Değerlendirilmesi

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ABSTRACT

Objective: Intravenous immunoglobulin (IVIg) is one of the most common biologic agents used in daily intensive care practice. Our aim in this study was to evaluate IVIg indications and side effects in patients hospitalized in the pediatric intensive care unit.

Method: The data of 116 patients who received IVIg treatment between 2014-2018 in a tertiary level pediatric intensive care unit were retrospectively evaluated.

Results: The patient group with the highest use of IVIg was found to have sepsis. The highest dose was detected in patients with Steven Johnson syndrome and the highest total dose was detected in patients with secondary immunodeficiency. Use of IVIg in off-label diseases was found more than use by indication.

Conclusion: IVIg is a life-saving treatment in selected patients and clinical conditions. In our study, the most common disease group in which IVIg was used and concomitant highest mortality was found to be sepsis. In off-label diseases, especially in sepsis, the use of IVIg can be reduced with alternative treatments.

Keywords: Intravenous immunoglobulin, pediatric intensive care, sepsis

ÖZ

Amaç: İntravenöz immünoglobulin (İVİg), günlük yoğun bakım pratiğinde kullanılan en yaygın biyolojik ajanlardan biridir. Bu çalışmada amacımız çocuk yoğun bakım ünitesinde yatan hastalarda İVİg endikasyonlarını ve yan etkilerini değerlendirmektir.

Yöntem: Üçüncü basamak çocuk yoğun bakım ünitesinde, 2014-2018 yılları arasında İVİg tedavisi almış 116 hastanın verileri retrospektif olarak değerlendirildi.

Bulgular: İVİg kullanımının en fazla olduğu hasta grubu sepsis olarak bulundu. En yüksek doz steven johnson sendromu hastasında, toplam en yüksek doz ise sekonder immün yetmezlikli hastalarda saptandı. Endikasyon dışı hastalıklarda İVİg kullanımı, endikasyon ile kullanımdan daha fazla saptandı.

Sonuç: İVİg, seçilmiş hastalarda ve klinik koşullarda hayat kurtaran bir tedavidir. Çalışmamızda en sık İVİg kullanılan ve mortalitenin en fazla olduğu hastalık grubu sepsis olarak bulunmuştur. Endikasyon dışı hastalıklarda, özelikle sepsiste, alternatif tedaviler ile İVİg kullanımı azaltılabilir.

Anahtar kelimeler: İntravenöz immünoglobulin, çocuk yoğun bakım, sepsis

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INTRODUCTION

Intravenous immunoglobulin (IVIg) preparations are biological products derived from human plasma used for their replacement and immunomodulatory effects on the immune system. IVIg is a biological agent containing a high rate (>95%) of polyclonal immunoglobulin G (IgG) obtained from plasma taken from a large number of healthy donors [(1)]. Igs are the main or supportive treatment option in the prevention and treatment of some post-transplant diseases, especially in primary immunodeficiencies, and in neurological and autoimmune-inflammatory

diseases [2]. In addition, with the discovery of its anti-inflammatory and immunomodulatory effects, it has been shown to be protective or therapeutic in many diseases [3]. Despite its increasing use, IVIg is known to be administrated in some diseases with a low level of evidence. It should be used with caution in selected cases due to the difficulties encountered in obtaining IVIg and its cost, as well as its side effects. In this study, we have evaluated IVIg indications, doses and side effects in patients hospitalized in our pediatric intensive care unit.

MATERIALS and METHODS

Study Design

The study was conducted retrospectively with the data of patients hospitalized in a 24-bed tertiary level pediatric intensive care unit between January 2015 and January 2019 in a training and research hospital. The study was approved by the University of Hatay Mustafa Kemal University Ethics Committee (approval number: 27, date: 12.11.2020).

Study Population

Patients aged between 1 month and 18 years who received IVIg treatment in the pediatric intensive care unit were included whereas patients younger than one month and older than 18 years of age, and patients who were discharged or died within the first 24 hours, and those with missing data required for the study were excluded from the study.

The medical records of the patients who received IVIg treatment during intensive care unit hospitalization were retrospectively reviewed, and demographic data, hospitalization diagnoses, number and doses of IVIg treatment received, side effects and prognosis were recorded. Informed consent was obtained from the families of the patients.

The primary endpoint of the study was length of stay, and the secondary endpoint was mortality. Side effects associated with IVIg infusion are classified either as acute and delayed reactions during infusion or as mild/moderate/severe reactions within the clinical classification.

Acute and delayed reactions are classified as follows;

1. Acute reactions: Headache, nausea, myalgia, fever, chills and chest pain, skin findings such as rash redness, and signs of anaphylaxis.

2. Delayed reactions: Migraine-type headache, aseptic meningitis, kidney injury, thrombotic events, hemolysis, neutropenia, transfusion-associated acute lung injury.

Side effects are also clinically classified as mild, moderate or severe as follows;

1. Mild reactions: These include headache, rash, muscle aches, chills, feeling sick, itching, urticaria, anxiety, dizziness, unsteadiness or nervousness. It can be controlled by reducing the infusion rate.

2. Moderate reactions: Includes mild reactions that worsen or other symptoms such as chest pain or wheezing that require discontinuation of the infusion.

3. Severe reactions: These include persistent or worsening moderate reactions or other symptoms such as tightness in the throat, severe headache and chills, severe shortness of breath or wheezing, severe dizziness or fainting, chest pressure or collapse. Severe reactions require medical attention by stopping the drug infusion.

All medications used in our study contained 5% IVIg concentration, at least ≥95% of IgG and additionally maltose as a stabilizing agent. After IVIg solutions were diluted 1:1 with 5% dextrose, it was started at a rate of 0.02 mg/kg/min and was administered at a rate of 0.08 mg/kg/min by increasing the dose if no side effects were observed within 15-30 minutes. No routine premedication was applied to the patients before IVIg administration.

Statistical Analysis

The data were transferred to the SPSS 22.0 program. Distributions of numerical variables were analyzed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mean ± standard deviation or median/interquartile range (IQR) was used as a measure of distribution. Since the numerical data were not normally distributed, non-parametric tests were applied. The Mann-Whitney U test was used to compare the means of two independent groups. Results with a p-value below 0.05 were considered statistically significant.

RESULTS

One hundred and sixteen of 130 patients who received IVIg during the study period were included in the study. Ten patients died within the first 24 hours, and 4 more patients were excluded from the study because their medical data were missing. Sixty (51.7%) of 116 patients were male and 56 (48.3%) were female.

Average age and weight were 23 (IQR: 65) months and 11.55 (IQR: 18.5) kilograms, respectively. Sepsis was the most common (23.3%, n=27) in ten disease groups. According to the primary disease, a total of 56 (48.2%) patients [primary immunodeficiency, secondary immunodeficiency, idiopathic thrombocytopenic purpura (ITP), Kawasaki disease] received IVIG with indication, while the remaining 60 (51.7%) patients (sepsis, myocarditis, encephalitis, Guillain Barre syndrome, acute disseminated encephalomyelitis (ADEM): Steven Johnson syndrome (SJS) was found to have received IVIg with evidence-based methods without any indication.

Respiratory distress, sepsis and shock, neurological diseases and renal problems were found to be the most common reasons for admission to the intensive care unit in patients with primary and secondary immunodeficiency, respectively.

The demographic data of the patients are shown in Table 1, and the use of IVIg by indication and evidence category is shown in Table 2.

Side effects were observed in 17 patients in our study (14.65%). There was no significant difference between genders in terms of side effects (p=0.137). The patient group with the most common side effects were those with primary immunodeficiency. In our study, the most common side effects were flushing and rash observed in four patients, while fever was the second most common and observed in three patients. Mild hypotension was observed in two patients and chest pain observed in one adolescent patient. Side effects of diseases are given in Figure 1.

Table 2. Use of IVIg by indication and evidence category

Indication	Number of cases (n, %)	Level of evidence
FDA-approved indications		
Primary immundeficiency	26	Iıb
Agammaglobulinemia	4	Iıb
CVID	6	III
Hiper IgM	3	III
Hiper IgE	3	III
IgG subclass deficiency	10	
ITP	-	Ia
Kawasaki disease	-	Ia
Evidence-based indications		
Sepsis	27	III
Seconder immundeficiency	25	
Acute lymphoblastic leukemia	11	IV
Acute myeloid leukemia	8	IV
Lymphomas	4	IV
Neuroblastoma	2	IV
Encephalitis	15	III
Myocarditis	13	III
Guillain Barre syndrome	2	Ib
ADEM	2	III
SJS	1	Iıa

IVIg: Intravenous immunoglobulin, CVID: Common variable immun deficiency, ITP: Immune thrombocytopenic purpura, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome, IgG: Immunoglobulin G, FDA: The United States Food and Drug Administration

Table 1. Demographic and clinical findings

Parameter	Age (month)	Weight (kg)	n (%)
Primary disease			
Sepsis*	8 (18)	7.25 (7.1)	27 (%23.3)
Primary immunodeficiency*	15.50 (29)	9.5 (8.87)	26 (%22.4)
Secondary immunodeficiency*	60 (116)	30 (23.5)	25 (%21.6)
Encephalitis*	49 (99)	17.65 (25.50)	15 (%12.9)
Myocarditis*	6 (32)	6.25 (11.25)	13 (%11.2)
ITP**	21 (7-25)	13.90 (8.1-14.5)	3 (%2.6)
Kawasaki dissease**	23.50 (21-26)	11.8 (10.6-13)	2 (%1.7)
Guillain Barre syndrome**	83.5 (47-120)	28.25 (17.5-39)	2 (%1.7)
ADEM**	67 (62-72)	28 (27-29)	2 (%1.7)
SJS	96	25	1 (%0.9)

*Median (IQR): Interquartile range, **Median (minimum-maximum), age and weight given as Steven Johnson syndrome is one patient. ITP: Immune thrombocytopenic purpura, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome

Considering the mortality rates, 14 patients were found to have died (12.06%). The most common mortality was seen in sepsis patients (6 exitus), primary immunodeficiency (4 exitus), secondary immunodeficiency (3 exitus), and myocarditis (1 exitus) patients, respectively.

The most IVIg was used for the patients with SJS, the second most common reason to use IVIg was Guillain Barre syndrome and the third was ADEM. There were a total number of 5 patients in these three disease groups. The disease group with the highest amount of IVIg use, in general, was found to be secondary immunodeficiencies. The second most common disease group was found to be encephalitis. The lowest dose used in our study was 400 mg/kg, while the highest dose was 1,000 mg/kg (Table 3).

DISCUSSION

While IVIg was first used in patients with primary immunodeficiency in 1981, it is now widely used in the treatment of many autoimmune diseases and systemic inflammatory diseases [4].

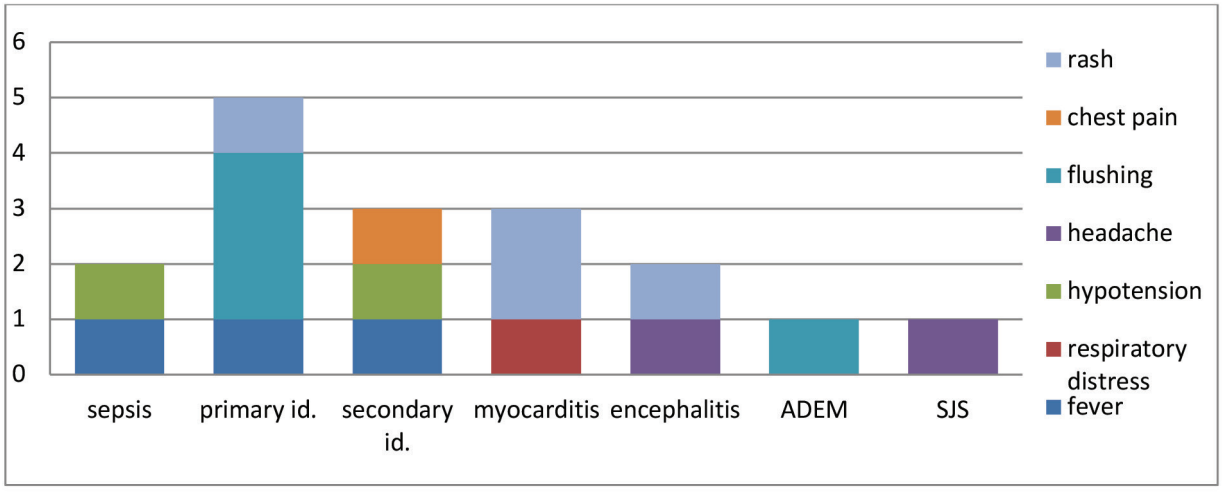

Figure 1. Side effects according to diseases

Primary id: Primary immundeficiency, Secondary id: Secondary immundeficiency, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome

Table 3. Total amount of IVIg used by disease groups

Parameter	Number of cases (n)	IVIg dose (mg/kg) (minimum-maximum)	Number of doses of IVIg (n) (minimum-maximum)	Total amount of IVIg (grams) [median (IQR)]
Primary disease				
Sepsis	27	400-1000	1-2	6.5 (5.7)
Primary immundeficiency	26	400-800	1-5	10 (15.6)
Secondary immundeficiency	25	400-600	1-5	30 (41.9)
Encephalitis	15	1000	1-2	31.6 (48)
Myocarditis	13	1000	1-2	12.6 (11.6)
ITP	3	1000	1-2	17.4 (8.1-25)*
Kawasaki disease	2	2000	1	18.3 (10.6-26)*
Guillain Barre syndrome	2	400	5	56.5 (35-78)*
ADEM	2	400	5	56 (54-58)*
SJS	1	400	5	80*

IVIg: Intravenous immunoglobulin, IQR: Interquartile range, ITP: Immune thrombocytopenic purpura, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome, Due to the low number of cases for ITP, Kawasaki disease, Guillain Barre, ADEM and SJS, minimum-maximum values were given instead of IQR for the total amount of IVIg

The effects of IVIg include complex mechanisms [5]. It shows its main effect by destroying nonspecific Fc receptors in the mononuclear phagocytic system or by preventing the binding of immune complexes to Fc receptors in cells [6]. In addition, it prevents the activation of the cascade by interacting with complement and cytokines, decreases the dendritic cell effect, prevents T and B-lymphocyte activation and differentiation [7,8].

IVIg indication is basically divided into two categories as evidence-based and non-evidence based [9]. Based on the evidence, IVIg use has been granted by the FDA (The United States Food and Drug Administration) for the following seven diseases. These diseases are listed as follows;

1. Primary immunodeficiency treatment,
2. Prevention of recurrent infections caused by B-cell chronic lymphocytic leukemia and bacterial infections in patients with hypogammaglobulinemia,
3. Prevention of coronary artery aneurysms in Kawasaki disease,
4. Prevention of infections, pneumonia and acute graft versus host disease after bone marrow transplantation,
5. Reducing severe bacterial infection in human immunodeficiency virus-infected children,
6. Increasing the number of platelets in ITP, preventing or controlling bleeding,
7. Chronic inflammatory demyelinating polyneuropathy.

Apart from FDA approved indications, IVIg is also used in the treatment of diseases for which there is some uncertain evidence of its benefit [10]. For example, IVIg has been shown to increase left ventricular functions in pediatric patients with fulminant myocarditis [11]. It is thought to be beneficial by stopping spasms, unconsciousness, shortening the duration of neuropathic symptoms and fever in viral encephalitis, and reducing seizures in autoimmune encephalitis [12,13]. In studies evaluating the use of IVIg, it has been reported that IVIg is used as a treatment option in non-indicative diseases at a rate of 14% to 47% due to its clinical benefits, and its use has increased from past to present [14]. Similar to our study, in a recent study conducted retrospectively with 301 patient data, it was reported that only 56 patients received IVIg with FDA-approved indications, and other patients were given IVIg with low-level of evidence indications [15]. Current studies show that the use of IVIg increases in all disease groups, especially in off-label diseases. In our study, we found that the most common IVIg was used in the sepsis patients (n=27, 23.3%), and similar to the literature data, the use of off-label IVIg was more often than its labeled use. In addition, sepsis was the second most common reason for intensive care hospitalization in primary and secondary immunodeficiency patients. This was explained by the fact that our hospital is the largest pediatric intensive care clinic in the region, and that patients with a specific diagnosis were referred to our hospital. Table 2 presents the diseases in which IVIg is used according to indication and evidence category.

It is known that IVIg in sepsis increases passive immunity through neutralization of bacterial toxins, increasing opsonization of bacteria and inhibition of immune cell proliferation and inflammatory cytokines [16]. It has been reported that IVIg treatment in patients with sepsis and septic shock reduces the course of advanced treatment methods in patients hospitalized in the intensive care unit or is used as a rescue therapy [17]. Although IVIg treatment is not recommended routinely in the treatment of sepsis in children, the current sepsis guideline leaves its use in selected patients, even with a low level of evidence, to the preference of the clinician [18].

It is clinically important to determine which patients will generally benefit most from IVIg therapy in patients with sepsis. However, studies investigating immunomodulatory treatment approaches in the treatment of sepsis generally do not specify a definite classification of suitable patients [19,20]. In our study, IVIg treatment was applied to severe sepsis patients who developed more than two organ dysfunctions while they were hospitalized with the diagnosis of sepsis. In these patients, due to the severity of inflammation caused by sepsis, the development of multiorgan failure is common and the high mortality rates associated with this multiorgan failure, therefore, IVIg treatment was applied considering that they could benefit from this treatment due to its anti-inflammatory properties.

It is thought that lymphopenia developing in septic and therefore Ig deficiency is associated with increased mortality and the mortality of septic shock is more than 50% [21]. In a meta-analysis from 8 studies involving 492 patients using IVIg for the adjuvant treatment of bacterial sepsis or septic shock, IVIg treatment was reported to be associated with a significant reduction in mortality [22]. In our study, mortality was 22.2% in septic patients who received IVIg treatment. Compared to these data,

although the mortality rate in sepsis patients is low in our study, the effect of IVIg to this rate cannot be clearly demonstrated.

Although the dose and duration of IVIg treatment varies depending on the disease, it can be used as replacement therapy (low dose: 200-400 mg/kg) and immunomodulator-anti-inflammatory therapy (high dose: 1-2 g/kg) [23]. Considering the amount of IVIg used according to disease groups in our study (Table 3), it was seen that the highest amount of IVIg was used in Steven Johnson's patient and the highest total amount was used in secondary immunodeficiency patients. This situation was found to be related with the high number and weight of patients with secondary immunodeficiency. Although the SJS group received a very high dose of IVIg, there was only one patient in this disease specific group. The minimum and maximum IVIg doses used in our study were found to be 400-1000 mg/kg.

IVIg therapy is generally a relatively safe treatment with mild side effects [24]. Although numerous clinical studies have shown that Ig is effective and well tolerated, various side effects have also been reported. Generally, mild to moderate reactions occur in 5% to 15% of infusions [25]. Side effects may develop due to patient-induced factors or the content of the IVIg preparation. Most can be controlled by slowing the infusion rate. In addition, the dose and concentration of IVIg and the daily dose should be carefully adjusted [26]. In our study, flushing and rash were the most common side effects in four patients, while fever which was seen in three patients was the second most common side effect. There was mild hypotension in two patients and a feeling of chest pain in one adolescent. When IVIg infusion was interrupted, the complaints regressed. These complaints seen in three patients did not recur when the treatment was continued by reducing the infusion rate. electrocardiogram was normal in these patients due to chest pain. When the infusion was interrupted or the infusion rate was decreased in patients who developed side effects, the indicated side effects regressed.

Knowing what mild to serious side effects to expect in the application of immune globulin therapy can prepare both the patients and the clinicians for treatment changes to reduce their effects [27]. In addition, while the mortality was higher in the study group than our intensive care overall mortality rate, this was attributed to the fact that the study was conducted in the most critically ill patients.

IVIg is used frequently in pediatric intensive care, in cases of open and unclear indications. Regulations should be made for access to IVIg in the indication list within the scope of national health planning and the conditions required for IVIg use should be explained. The criteria for clinical use of IVIg should be more clearly defined. There is a need for up-to-date protocols developed for clinicians to help determine the appropriate IVIg use and indications.

Targeted treatment of patients who would potentially benefit from IVIg therapy, based on evidence-based criteria, should be made in a non-discriminatory approach. Unfortunately, with the available data it is difficult to interpret a reliable and validated assessment of cost-effectiveness in relation to total treatment costs for diseases using labeled and off-labeled IVIg.

The continued substantial annual growth in IVIg use, its relatively high cost, and difficulty in procuring require health policy to remain consistent with an evidence-based approach to IVIg use. In order to confirm the rationale for the use of IVIg presented in this study and to target the treatment to the right patient group, at the right time, at the appropriate dose and in an optimal period, detailed studies are needed to investigate the effect of IVIg on mortality and length of stay on a disease basis which may preferably compare alternative treatments and cost-effectiveness.

CONCLUSION

IVIg is a life-saving treatment in selected patients and clinical conditions. However, the necessary indications should be selected carefully due to the side effects and cost. Treatment guidelines can be updated by the use of other immunomodulatory treatments such as corticosteroids and plasma exchange in sepsis, encephalitis and myocarditis where IVIg is frequently used, and by determining the effectiveness of these alternative therapies.

Ethics

Ethics Committee Approval: The study was approved by the University of Hatay Mustafa Kemal University Ethics Committee (approval number: 27, date: 12.11.2020).

Informed Consent: Informed consent was obtained from the families of the patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: F.S., G.A., Concept: F.S., H.A., Design: H.A., Ö.S.S., Data Collection and/or Processing: F.S., Ö.S.S., Analysis and/or Interpretation: F.S., G.C., Literature Search: F.S., G.A., H.A., Writing: F.S., G.A., G.C., Ö.S.S., H.A.

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