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Immediate adverse reactions to intravenous immunoglobulin in children: a single center experience

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Key words
Intravenous immunoglobulin; adverse events

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Summary
Intravenous immunoglobulin (IVIG) is commonly used in primary and secondary immunodeficiency diseases as well as autoimmune conditions as immunomodulatator treatment. Immediate adverse events which are generally mild and occur during infusion are seen in 6 hours. Reported immediate adverse events are in a wide range from 1%-40% in pediatric patients. 115 patients who received IVIG (except newborns) were included into this crosssectional study. IVIG was given to patients for primary immunodeficiencies (n=8), ITP (n=65), Kawasaki disease (n=11), secondary immunosupression (n=28), and passive immunization (n=3). 5%, 10% IVIG preparations and pentaglobin were used. Headache, fever, chills, nausea, rash, arthralgia, myalgia and back pain were accepted as mild immediate events. There were 62 (54%) boys and 53 (46%) girls aged 1 month-18 years. Mean age of the group was 7.4±4.6 years. Immediate adverse events due to IVIG infusions were seen in 29 (25.2%) of all patients. Gender and types of the disease were not different in significance regarding the presence of adverse events. The rate of adverse events did not change with receiving pre-medication. The most common reaction was fever/chills. Immediate reactions were seen in first 6 hours in 7 patients and during infusion in the remaining. They were treated with slowing of the infusion rate and infusion was stopped in 3 patients because of moderate events. Because of the increasingly use of IVIG therapy, it is important to know the side effects. High doses, high infusion rates, accompanying infection may worsen the adverse effects especially in primary immunodeficiency diseases.

Introduction

Intravenous immunoglobulin (IVIG) has been widely used for treatment since 1981 (1). Its area of usage is widening such as prophylaxis and replacement therapy for primary and secondary immunodeficiencies and for immunomodulatory effects in autoimmune and inflammatory conditions such as immune trombocytopenic purpura (ITP), Kawasaki disease, and Guillain-Barré syndrome (2,3).
IVIG is a biologic product prepared from donor serum pool after a series of procedures such as ethanol fractionation and adding stabilizers (4). Although these steps remove immunoglobulin aggregates, adverse events are seen frequently (5). Adverse reactions with IVIG infusions vary from 1% to 81%, but mostly about a rate of 20% (3,6). These events can be classified as immediate, delayed and late adverse effects. Immediate adverse events such as fever, headache, arthralgia, flushing, rash, acute renal failure, anaphylaxis, hemolysis due to IVIG are seen in the first 6 hours of the infusion, delayed adverse events develop in 72 hours to 1 week and late events can be seen in weeks to months after IVIG administration. Reported immediate adverse events are in a wide range from 1-40% in pediatric patients (7-11). These reactions are generally mild and occur during infusion (12).
IVIG preparations differ in their composition and properties, and these factors can affect the efficacy and tolerability of IVIG. They are prepared at various concentrations with 5%, 10% and 3-12% (8).
In the present study, we aimed to evaluate the frequency of immediate adverse reactions due to IVIG infusions in patients received IVIG mostly due to autoimmune diseases.

Materials and Methods

This study was conducted between January 2009 and December 2009 in a tertiary referral center in Istanbul. One hundred and fifteen patients who received IVIG in pediatric clinics (except newborns) were included, and a cross-sectional study was performed. In patients who were receiving IVIG infusions on a regular basis, only one infusion was included in the study. IVIG was given to patients for primary immunodeficiencies (n = 8), ITP (n = 65), Kawasaki disease (n = 11), secondary immunosuppression (n = 28), and passive immunization (n = 3).

Headache, fever, chills, nausea, rash, arthralgia, myalgia and back pain were accepted as mild immediate events; wheezing, chest pain as moderate and anaphylaxis, hypotension, cardiovascular events, altered mental status as severe reactions.

Demographic data (age, gender), co-morbid diseases, history of reactions to blood products / IVIG were taken from the parents and their primary clinicians.

IVIG preparations at concentrations with 5% and 10% and pentaglobin were used. Infusion rates were between 3-10 ml/kg/hour. When mild reactions were seen, infusion was paused temporarily and re-started after complete resolution of the symptoms. In the course of moderate and severe reactions, infusion was stopped totally.

Findings were analysed using chi-square test with SPSS 11.0 statistics programme, and difference was considered significant below the p = 0.005 level.

The local Ethics Committee of Bakirkoy Research and Training Hospital has approved the study.

Results

One hundred and fifteen patients (n = 115) were included into the study. There were 62 (54%) boys and 53 (46%) girls aged between 1 month - 18 years. Mean age of the group was 7.4 ± 4.6 years (median: 6 years).

Immediate adverse events due to IVIG infusions were seen in 29 (25.2%) of the patients. Some of them appeared during infusion, and some was reported by parents at the next visit. Demographic features, diseases requiring IVIG treatment and the rate of immediate adverse events were summarized in **table 1**. Gender and types of the diseases were not different in significance regarding the presence of adverse events (p = 0.278 and p = 0.936, respectively) (**table 1**). Strikingly, in primary immunodeficiency patients, percentage of adverse events was higher than the other groups in percentages (50% of the 8 patients). There was no significant association between the rate of adverse reaction and age in patients with primary immunodeficiency disorders.

Thirty-eight (33%) patients had received IVIG or other blood product infusions previously, and only 6 of them had mild reactions in previous infusions. Pre-medication with anti-histamines and anti-pyretics were performed in those 6 patients who described previous adverse reactions. In 3 of those 6 patients, adverse events recurred. Although the number of the patients was low, the rate of adverse events did not change with pre-medication (p = 0.16). In addition, previous history of receiving blood product and having reaction to IVIG or another blood product did not show significant difference in developing adverse events (p = 0.52, p = 0.68, respectively).

Ninety-five percent of the patients were treated with 5% IVIG preparations, so we could not perform statistical analysis between the other concentrations of IVIGs. **Table 2** shows the types of immediate adverse reactions to different IVIG preparations. There was no difference between various IVIG solutions regarding the types of immediate adverse reactions.

Table 1 *- Demographic features of patients and types of diseases.*

	Patient number (n, %)	Adverse reaction (n, %)	p
Gender			
Female	53 (46)	15 (28.3)	0.278
Male	62 (54)	14 (22.6)	
Replacement (0.4-0.5 gr/kg)			
Primary Immunodeficiencies	8 (7)	5 (62.5)	0.936
Secondary Immunosuppression[1]	28 (24)	3 (10.7)	
Immunomodulation (1-2 gr/kg)			0.936
Kawasaki Disease	11 (9.6)	2 (18.2)	
Autoimmune Diseases[2]	65 (56)	19 (29.2)	
Other[3]	3 (2.6)	-	

[1]Hemophagocytic hystiocytosis (HLH), Malignancy.
[2]Guillain-Barré Syndrome, Immune thrombocytopenic purpura (ITP).
[3]Passive immunization for measles exposure.

Table 2 *- Immediate adverse reactions and association with different IVIG preparations.*

n (%)	Octagam	Flebogamma	IgVena	Pentaglobuline	Tegeline	Kiovig	Total of all adverse events
Fever / Chills	4 (30.7)	8 (61.5)	1 (7.6)	-	-	-	13 (44.8)
Vomiting	4 (40)	3 (30)	2 (20)	-	-	1 (10)	10 (34.5)
Headache	2 (28.5)	2 (28.5)	2 (28.5)	-	-	1 (14.2)	7 (24.1)
Nausea	1 (3.5)	1 (3.5)	-	-	-	-	2 (6.9)
Rash	-	-	-	-	1 (3.5)	1 (3.5)	2 (6.9)
Wheezing	-	-	-	-	-	1 (3.5)	1 (3.5)
Ventricular fibrillation	-	-	-	1 (3.5)	-	-	1 (3.5)

Table 3 *- Adverse reactions according to types of diseases.*

n (%)	Kawasaki Disease	Autoimmune Diseases	Primary Immunodeficiencies	Secondary Immunodeficiencies	Total of all adverse events
Fever / Chills	2 (15.3)	8 (61.5)	2 (15.3)	1 (7.6)	13 (44.8)
Vomiting	-	9 (90)	-	1 (10)	10 (34.5)
Headache	-	7 (100)	-	-	7 (24.1)
Nausea	-	1 (50)	1 (50)	-	2 (6.9)
Rash	1 (50)	-	-	1 (50)	2 (6.9)
Wheezing	-	1 (100)	-	-	1 (3.5)
Ventricular fibrillation	-	-	-	1 (100)	1 (3.5)

The most common immediate adverse reactions were fever and chills (13% of the total adverse events). In 6 patients, more than one adverse reaction were observed such as fever and headache. During the first 5 minutes of pentaglobuline infusion, ventricular fibrillation and cardiac arrest developed in 1 patient, but this patient was in septic shock status and clinically unstable. When we look at the adverse events one by one, none of them differed according to types of the diseases ($p > 0.05$). But we saw that headache was only seen in patients receiving IVIG due to ITP (**table 3**). Moderate events were rare, only 1 patient developed wheezing. Mild reactions such as headache continued over 6 hours in 2 patients. Except for these one moderate and one severe reaction, all remaining adverse events were accepted as mild. Immediate adverse reactions were seen in the first 6 hours of infusion in 7 patients and during infusion in the remaining 22 patients. They were treated with slowing of the infusion rate and infusion was stopped in 3 patients because of moderate events in 1 patient and not responding to slow the rate of infusion in 2 patients. Medical treatment with anti-histamine and/or anti-pyretic was required in 14 patients (48%) after adverse events occurred.

Discussion

The severity of the adverse events symptoms can be examined as mild, moderate and severe (8). We accepted mild reactions as headache, fever, nausea, emesis, flushing, muscle ache, chills, feeling sick, itching, urticaria, anxiety, light headedness, moderate reactions as chest pain, wheezing and worsening symptoms of mild reaction and severe reactions as persisting or worsening of moderate reactions and severe headache and shaking, severe breathlessness or wheezing, severe dizziness or fainting, sensation of pressure in chest or collapse. We evaluated only immediate adverse events in this study. Most of the patients developed only mild reactions. Severity of the adverse events were not found significantly different from the literature (13).

Mild reactions were subsided with decreasing the infusion rate, and it can also be managed by medications such as antihistamines, paracetamol and small doses of corticosteroids, but in moderate reactions it is necessary to stop the infusion. Adrenaline administration and further medical attention would be required in severe reactions. It was reported that adverse reac-

tions were frequently seen in non-primary immune deficiency patients (13). In our patients, although there was no difference between adverse events and types of diseases, the percentage of adverse events in primary immunodeficiencies were seen higher. Adverse reactions with IVIG infusions vary in wide range, but mostly about a rate of 20% (3,6). In our study, adverse events were seen at a rate of 25.2%, this finding was similar with the literature. Higher infusion rates are reported to be related to higher adverse events. Beginning the infusion slowly, and then increasing gradually, based on patient's tolerance, can prevent these reactions (14). In our study, as recommended, we started at minimal infusion rates and raised to 10 ml/kg/h to minimize the adverse effects. Unfortunately, because of the lack of previous data, we could not compare the infusion rate and adverse event rates.

In the literature, one of the most common adverse event was reported as persistent headache due to acute aseptic meningitis. Headache can be minimized by continuing IVIG therapy at a slow infusion rate and by hydration, antihistamines and analgesics (15). It is also suggested that there was a relationship between high and concentrated dose of IVIG and headache (15,16). We did not show a correlation between higher dose and more frequent headache. Headache was not the most common adverse effect in our study and this can be related to the less usage of the high concentrated IVIG preparations. The other most common adverse reaction is reported as fever (17). Fever was the most common adverse reactions in our study and this was compatible with the literature.

Bichuetti-Silva *et al.* also noticed in their study that some patients had more than one adverse reaction at the same infusion (13). Similar with this study, 6 patients (5%) had more than one adverse events in our study. Hamrock et al. reported that premedications before IVIG infusions may prevent the adverse reactions (18). In our study, 38 patients had received IVIG or blood product infusion previously, six of them have had adverse events more than one time despite premedication with diphenhydramine and acetaminophen before IVIG infusions, in half of them adverse events recurred. Premedication may reduce the incidence of adverse events and we suggest to use premedication especially in patients who are receiving IVIG regularly.

Existing infection during the infusions was reported as an important risk factor for IVIG adverse effects. The reason of this was explained the antigen-antibody complex formation during the infection. Adverse reactions occur probably due to aggregated immunoglobulin molecules which cause the complement system to be activated, antigen-antibody reactions, possible contaminants or even stabilizers that may have been used during the manufacturing process (17). In our study, IVIG was used for secondary immunosuppression in 28 patients and passive immunization for measles in 3 patients. Unlikely, despite severe infections in secondary immunosuppressive patients, existing infection did not increase the rate of adverse events.

In summary, because of the increasingly use of IVIG therapy, it is important to know the adverse events. It should be kept in mind that adverse events to IVIG might be more frequent and severe with high dose, high infusion rates, during infection period and especially in primary immunodeficiency diseases. In addition, records related to IVIG infusions should be noted properly to set the infusion rates and doses in the next infusions.

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