Adverse reactions of prophylactic intravenous immunoglobulin infusions in Iranian patients with primary immunodeficiency

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Background: Although long-term intravenous immunoglobulin infusion is an effective treatment for children with antibody deficiencies, it can be complicated by systemic adverse reactions.

Objective: To evaluate the adverse reactions of intravenous immunoglobulin therapy in patients with primary immunodeficiency.

Methods: Seventy-one immunodeficient patients receiving intravenous immunoglobulin were evaluated during a 7-year period (1995–2002) at Children's Medical Center in Tehran, Iran. Immunological diagnoses were as follows: common variable immunodeficiency (31 patients), X-linked agammaglobulinemia (25 patients), IgG subclass deficiency (5 patients), hyper-IgM syndrome (2 patients), and ataxia-telangiectasia (8 patients).

Results: One hundred fifty-two cases (12.35%) of adverse reactions occurred following 1,231 infusions in 35 patients. The most frequent immediate adverse reactions were mild reactions (131 infusions), including chills, fever, flushing, muscle pains, nausea, headache, and anxiety. Moderate reactions, such as vomiting, chest pain, and wheezing, occurred in 19 infusions. Two patients experienced severe adverse reactions. The highest proportion (23.06%) of reaction to injection was in patients with common variable immunodeficiency.

Conclusions: Intravenous immunoglobulin is a well tolerated medical agent for patients with antibody deficiency. However, to prevent occurrence of immediate adverse reactions during infusion in these patients, physicians should perform a detailed history and proper physical examination and check the titer of anti-IgA.

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INTRODUCTION

Immunoglobulin replacement therapy is an essential treatment in patients with antibody deficiencies.[1,2] Failure to provide an adequate replacement therapy results in an increase in mortality and long-term morbidity.[3–6] Human immunoglobulin was first introduced as a therapeutic modality by Bruton,[7] following his description of the first case of X-linked agammaglobulinemia in 1952. Subsequently, clinical indications for immunoglobulins were developed for other primary immunodeficiencies and selected cases of secondary antibody deficiency.[8,9] Antibody replacement was administered intramuscularly until the 1980s, when intravenous immunoglobulin (IVIG) products were introduced. Since that time, intravenous administration has become an acceptable route of administrating immunoglobulin.[2,10]

The availability of IVIG therapy in 1981 allowed a considerably high dose of IVIG to be administered, after which the IgG level could be normalized. Several published comparative trials documented the value of these higher doses in curtailing mild or severe infections.[11,12] Although IVIG therapy is clearly beneficial in certain conditions, it is not an absolutely safe therapeutic modality. There are some adverse reactions and complications, since IVIG is a biological product derived and purified from blood or plasma donation products.[13,14] Adverse reactions of IVIG can be divided into 3 types: immediate (occurring during the infusion), delayed (occurring hours to days after initiation of the infusion), and late. The most common form, however, is immediate adverse reactions that can be mild, moderate, or even severe.[15,16] The purpose of the present study is to evaluate immediate adverse reactions of IVIG infusion in patients with antibody deficiency.

METHODS

Study Design

This retrospective study conducted during a 7-year period was designed to monitor every adverse reaction that occurred while patients received IVIG at Children's Medical Center (a tertiary center for primary immunodeficient patients in Tehran, Iran).[17]

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Table 1. Number of Infusions and Reactions in Patients with Primary Immunodeficiencies

Disease	No. of patients	No. of patients with reactions	No. of infusions	No. of reactions	Proportion of reactions to infusions, %
Common variable immunodeficiency	31	21	542	125	23.06
X-linked agammaglobulinemia	25	8	470	18	3.83
IgG subclass deficiency	5	1	61	1	1.64
Hyper-IgM syndrome	2	1	51	1	1.96
Ataxia-telangiectasia	8	4	107	7	6.54
Total	71	35	1,231	152	12.35

Patients

Seventy-one primary immunodeficient patients (51 males and 20 females), whose conditions were diagnosed by standard criteria,[10,17] were treated with IVIG during a 7-year period (1995–2002). Their ages ranged from 2 to 30 years (mean ± SD age, 13.8 ± 5.5 years). Half of our patients were younger than 13 years. The investigated group included 31 patients with common variable immunodeficiency (CVID), 25 patients with X-linked agammaglobulinemia, 5 patients with IgG subclass deficiency, 2 patients with hyper-IgM syndrome, and 8 patients with ataxia-telangiectasia (Table 1).

Method of Infusions

All patients received human immunoglobulin, licensed for intravenous administration, every 3 to 4 weeks. The dose administered was between 400 and 500 mg/kg monthly. Six types of IVIG preparations were administered to our patients, including Nordimmun (HemaSure, Gentofte, Denmark), Sandoglobulin (Sandoz Pharmaceuticals Corp, Hanover, NJ), Intraglobulin (Biotest Pharma, Dreieich, West Germany), Gammonativ (Pharmacia and Upjohn, Stockholm, Sweden), Vigam (Bio Products Laboratory, Hertfordshire, United Kingdom), and Venoglobulin (Alpha Therapeutic Corp, Los Angeles, CA). These products were randomly coded as A, B, C, D, E, and F. While receiving IVIG, all patients were observed by a clinical immunologist (A.A.) and a nurse exclusively trained in IVIG therapy. Any adverse reaction was recorded in a special questionnaire that was designed for this study.

Classification of Reactions

Immediate adverse reactions of IVIG were categorized into 3 groups using the following criteria: mild reactions, including headache, flushing, chills, nausea, anxiety, muscle aches, and fever, necessitating the infusion to be slowed or stopped but then subsiding quickly, allowing the infusion to be restarted; moderate reactions, including chest pain, wheezing, vomiting, and other mild symptoms that rapidly worsened or recurred, necessitating the infusion to be discontinued; and severe reactions manifested by severe headache, severe chest pain, severe wheezing, sensation of pressure in the chest, and other moderate symptoms that persisted or rapidly worsened, necessitating the infusion to be discontinued, adrenaline administered, and medical attention sought.[2,9,16,18]

Statistical Methods

Univariate analysis was accomplished using the SPSS statistical software package, version 10.0 (SPSS Inc, Chicago, IL), and multivariate logistic regression analysis was performed using STATA statistical software, version 7.0 (StataCorp, College Station, TX).

RESULTS

Among the 1,231 IVIG infusions, 152 (12.35%) were associated with adverse reactions in 35 patients (Table 1). The rate of adverse reactions varied among patients with varied diagnoses (Table 1). The highest proportion of reactions to infusions were in patients with CVID (23.06%), in which reactions occurred in 125 injections (Table 2). This difference was statistically significant, after eliminating the confounding effects of age and sex (odds ratio, 6.50; 95% confidence interval, 2.95–14.35; $P < .001$). There were no differences in the incidences of adverse reactions among different preparations used (Fig 1).

Patients were divided into 2 groups based on serum IgA levels: patients with serum IgA levels less than 5 mg/dL (33 subjects) and patients without IgA deficiency (38 cases). The proportion of adverse reactions to infusions in IgA-deficient patients was 16.7% (109 of 654), which was higher than the other group (7.5%). This difference was statistically significant ($P < .001$). The mean ± SD serum IgG level in all patients was 312.9 ± 285.9 mg/dL. The association between serum IgG level and development of adverse reactions was not statistically significant ($r = -0.029$, $P = .81$).

Table 2. Adjusted Odds Ratios of Reactions in Different Diseases According to Sex and Age*

Variable	OR (95% CI)	*P* value
Common variable immunodeficiency	6.50 (2.95–14.35)	<.001
IgG subclass deficiency	0.27 (0.015–4.76)	.37
Hyper-IgM syndrome	0.37 (0.04–3.09)	.36
Ataxia-telangiectasia	1.25 (0.38–4.09)	.70
Sex	0.62 (0.27–1.44)	.27
Age	0.95 (0.89–1.006)	.08

Abbreviations: CI, confidence interval; OR, odds ratio.

* Reference category for diseases is X-linked agammaglobulinemia disease.

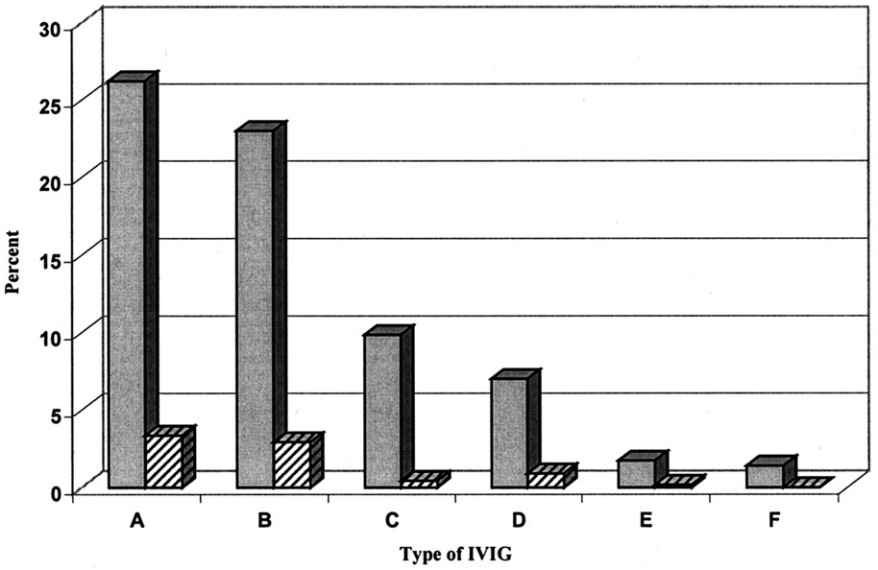

Figure 1. The percentage of different intravenous immunoglobulin (IVIG) product infusions and reactions among 1,231 injections in 71 patients with primary immunodeficiency. The following 6 types of IVIG preparations were administered and randomly coded as A, B, C, D, E, and F: Nordimmun, Sandoglobulin, Intraglobulin, Gammonativ, Vigam, and Venoglobulin.

Mild adverse reactions were observed in 131 cases (10.64%) and included chills, fever, flushing, muscle aches, nausea, headache, and anxiety in 33 of 71 patients (Table 3). Occurrence of mild adverse reactions in 49 of 131 infusions was associated with rapid infusions (more than 0.07 mL/kg per minute) and in 10 of 131 with untreated infections (5 cases of acute otitis media, 3 cases of acute sinusitis, 1 case of pneumonia, and 1 case of acute diarrhea). All of these symptoms subsided by slowing the rate of IVIG infusion and resolved without any further interventions.

Moderate adverse reactions occurred in 19 cases (1.54%) and included vomiting, chest pain, and wheezing in 12 of 71 patients (Table 3). Antihistamines and corticosteroids were administered to treat such adverse reactions.

Severe adverse reactions occurred in 2 (0.16%) of 152 reactions, including severe chest pain, severe wheezing, and severe headache (a 13-year-old boy with X-linked agammaglobulinemia and a 17-year-old girl with CVID, both having serum IgA levels of less than 5 mg/dL).

Table 3. Types of Reactions Observed among 152 Adverse Reactions Occurring in 37 Patients

Reaction	No. (%) of Reactions
Chills	90 (59.2)
Fever	24 (15.8)
Flushing	21 (13.8)
Muscle aches	21 (13.8)
Nausea	12 (7.9)
Headache	12 (7.9)
Vomiting	8 (5.3)
Anxiety	7 (4.6)
Chest pain	7 (4.6)
Wheezing	6 (4.0)
Severe chest pain	2 (1.3)
Severe wheezing	2 (1.3)
Severe headache	1 (0.7)

Six types of IVIG preparations were administered to our patients; however, 53 patients (74.6%) did not receive the same type of product for the entire treatment period. The IVIG product was changed in 121 infusions performed, and adverse reactions occurred in 18 of these injections (14.9%). This proportion of reactions to infusions was higher than other infusions (12.1%), but this difference was not statistically significant.

The proportion of adverse reactions during the first infusions and subsequent infusions were 11.3% (8 of 71) and 12.4% (144 of 1,160), respectively. There were no statistically significant differences. Among the 627 infusions in the first year, 91 adverse reactions occurred (14.5%), which was higher than the 10.1% in the following years (61 of 604). This difference was statistically significant ($P = .02$).

DISCUSSION

This study examined the adverse reactions caused by IVIG during immunoglobulin replacement therapy in 71 patients with primary antibody deficiency. Of 1,231 infusions of IVIG, 152 infusions (12.35%) were associated with adverse reactions in 35 of the 71 patients. Most of the immediate adverse reactions were mild (131 of 152 reactions). Lee et al[19] reported that 10% of the adverse reactions were noted in 13 cases, among which headache and fever were found to be more prevalent.

Bjorkander et al[20] have determined the rate of adverse reactions in 34 immunodeficient patients following 1,040 infusions of IVIG. Of 1,040 infusions, 49 (4.7%) were associated with adverse reactions, which had been observed in 12 of the 34 patients and included flushing, nausea, and head-

ache. In 4 cases, rapid infusion was associated with adverse reactions.

In our study, occurrence of mild adverse reactions in 49 of 131 infusions with adverse reactions was due to rapid infusion, which subsided by slowing the rate of infusion. These data show that mild adverse reactions do not necessitate that the infusion be stopped but rather that the rate be slowed until the symptoms subside.

Sudden adverse reactions during the treatment are almost always a result of the extremely rapid infusion rate,[21] highlighting the fact that infusion rate plays a significant role in preventing adverse reactions. It is strongly recommended that the infusion rate of IVIG be initiated no faster than 0.01 mL/kg per minute for the first 30 minutes, gradually increasing it a maximum rate of 0.07 mL/kg per minute only if well tolerated.[21]

Notably, 10 of 131 mild adverse reactions in our study were associated with untreated infections. The presence of active untreated bacterial infection is a contraindication to IVIG infusion until the time when infection has been controlled by appropriate antibiotic therapy. If IVIG is infused in such circumstances, it may lead to an immune complex formation that can result in severe adverse reactions.[20] It is therefore advisable to administer antibiotic therapy within a period of 2 days to control the infusion before starting IVIG therapy in such patients.

Moderate adverse reactions were noted in only 19 (1.53%) of the 1,242 infusions in 12 patients. These reactions did not subside by slowing the rate of IVIG administration. The presence of moderate reactions, such as chest tightness, mild wheezing, or vomiting, indicates that the infusions have to be discontinued. Antihistamines, aspirin, indomethacin, or hydrocortisone may be used as a prophylaxis or treatment protocol for such adverse reactions.[2,22]

In our study, the proportion of adverse reactions to infusions in patients with IgA deficiency was significantly higher than in other studies. In another study,[23] in which the serum levels of anti-IgA antibodies of patients undergoing IVIG therapy (including 3 CVID patients with moderate adverse reactions in this study) had also been measured, the titer ratio of serum IgG/anti-IgA antibody levels to total antibody levels in these 3 patients was significantly higher compared with those patients receiving IVIG. These 3 patients had serum IgA levels less than 5 mg/dL.

Patients with primary antibody deficiencies may develop anti-IgA antibodies after infusion of blood, plasma products, or immunoglobulin containing IgA.[24–27] In a study by Burks et al,[28] 3 patients with very high and progressive titers of anti-IgA antibodies have been described in whom life-threatening, anaphylactic reactions occurred after infusion of a few milliliters of immunoglobulin containing IgA. IgA-depleted preparations of intravenous gammaglobulin have to be administered to patients with very high or rising titers of anti-IgA antibodies.[29,30]

As noticed in our study, severe adverse reactions were extremely rare.[16] The highest proportion of adverse reactions (125 of 152) occurred in 21 (68%) of 31 CVID patients. This observation indicates that CVID patients could be more susceptible to adverse reactions that are more likely to be due to the development of autoantibodies[31–33] and IgG/anti-IgA antibodies.[34]

IVIG is a well tolerated agent for patients with antibody deficiency. The most important causes of adverse reactions following IVIG therapy include rapid infusion, the presence of active, untreated bacterial infections in patients on the day of infusion, and presence of anti-IgA antibodies. To prevent occurrence of immediate adverse reactions during infusion, it is therefore important to make sure that the patient is well before the infusion by taking a detailed history and performing a proper physical examination. In addition, in those patients with antibody deficiency who are planning on undergoing regular IVIG therapy, the titer of anti-IgA should be checked.

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