Adverse reactions associated with intravenous immunoglobulin therapy in patients with dermatologic diseases: An 11-year retrospective study

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INTRODUCTION

Intravenous immunoglobulin (IVIG) was developed more than 30 years ago. This treatment is currently approved for various conditions that include immunodeficiencies and autoimmune diseases. IVIG is a blood product that consists of polyvalent IgG antibodies pooled from at least 1000 different human donors. The main indication for IVIG in dermatology is to treat resistant autoimmune bullous diseases, especially pemphigus vulgaris. Treatment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are other indications.

IVIG is generally considered a safe, efficacious therapeutic modality. However, it is associated with a wide range of adverse effects. The reported incidence of adverse effects related to IVIG treatment in published literature varies from 2% to 81%. The most common adverse reactions include headache, nausea, myalgia, fever, chills, chest discomfort, and skin and anaphylactic reactions which can arise immediately during or after the infusion. Delayed events may be more severe and include migraine
headaches, aseptic meningitis, hemolysis, renal impairment, and thrombotic events. The aim of this study is to retrospectively review the frequency of adverse effects of IVIG therapy during an 11-year period at the Department of Dermatology, Razi Hospital, Tehran, Iran.

PARTICIPANTS AND METHODS

We reviewed medical records of 67 patients who received IVIG between April 2005 and March 2016. These patients received 94 IVIG infusions according to a published protocol on 3-5 consecutive days. We recorded information on sex, age, type of dermatologic disease, as well as early and delayed adverse reactions.

SPSS (version 19.0) was used for all statistical analyses. We used the t- and chi-square tests to assess the relationship between variables.

RESULTS

During this 11-year period, 67 patients received IVIG treatment. There were 40 (59.7%) male and 27 (40.3%) female patients. The patients had an average age of 38.1±14.1 years (range: 7-76 years). The patients received a total of 94 individual infusions of IVIG. Some patients received only one cycle of the IVIG infusion, whereas others received more than one cycle. Therefore, we presented the data according to IVIG infusion cycles. The average IVIG dose was 2.01±1.38 g/kg. Table 1 summarizes the patients’ dermatologic diseases and dosage of IVIG for each disease.

Table 1. Type of dermatologic disease treated with intravenous immunoglobulin (IVIG) and dosage of IVIG in each disease.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients (N)</th>
<th>Cycles (N)</th>
<th>Mean dosage of IVIG in each cycle (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>54</td>
<td>81</td>
<td>1.96</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mucous membrane pemphigoid</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SJS*</td>
<td>4</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>TEN**</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*SJS: Stevens-Johnson syndrome; **TEN: Toxic epidermal necrolysis

Table 2. Incidence of adverse events associated with intravenous immunoglobulin (IVIG) therapy.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Infusions, number (%)</th>
<th>Patients, number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in blood pressure</td>
<td>21 (22.3)</td>
<td>17 (25.3)</td>
</tr>
<tr>
<td>Fatigue and generalized weakness</td>
<td>5 (5.3)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (3.1)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (4.2)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3 (3.1)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3.1)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Decrease in blood pressure</td>
<td>2 (2.1)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (1.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1 (1.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>1 (1.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (2.1)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3 (3.1)</td>
<td>3 (4.4)</td>
</tr>
</tbody>
</table>

Table 2. Incidence of adverse events associated with IVIG therapy.
by chills in 2 patients. The average time of onset of fever was 2 hours and 20 minutes after the beginning of the infusion. The fevers responded to administration of acetaminophen in all 3 patients.

There were chills observed in 4 patients accompanied by fever in 2 patients. On average, the onset of chills was 2 hours and 7 minutes after the onset of the infusion. This adverse reaction was managed by temporary halting of the infusion and restarting at a lower rate after the resolution of chills.

Tachycardia and palpitations were reported in 3 patients and accompanied by an increase in blood pressure in 2 patients. On average, the tachycardia began approximately 45 minutes after the onset of the infusion. In these patients, the IVIG infusion was stopped and the patients received propranolol. The IVIG was restarted at a lower rate after resolution of the tachycardia.

Dizziness was observed in 3 patients, which began 3 hours and 40 minutes after the onset of the infusion on average. In one patient, the infusion was temporarily stopped and restarted after the dizziness resolved. Dizziness spontaneously resolved in 2 other patients after a few hours.

A decrease in blood pressure developed in 2 patients. The average time of onset was 1 hour and 45 minutes after the beginning of the infusion. In these patients, the IVIG infusion was stopped and the patients received intravenous infusions of normal saline. The IVIG resumed after normalization of blood pressure.

One patient developed a headache 5 days after the onset of IVIG. The headache was not severe in this patient and resolved without specific treatment.

Flushing was observed in one patient on the fifth day of the IVIG infusion. Flushing was treated with chlorpheniramine and reduction of the rate of the IVIG infusion.

One patient developed chest discomfort that was accompanied by an increase in blood pressure during the IVIG infusion. The infusion was stopped and the patient had an electrocardiography and measurement of cardiac enzymes. When a myocardial infarction was ruled out and the symptoms subsided, the IVIG infusion was restarted.

Hemolytic anemia was reported in one patient. Hemolysis developed 3 days after the end of the IVIG infusion. The patient’s hemoglobin level reduced to 9 g/dL. A serial complete blood count was performed to check hemoglobin levels, which gradually increased after a few days.

Leukopenia developed in 2 patients who received IVIG for the treatment of TEN on the third day of the IVIG infusion. The white blood cell count returned to normal after 3 days in both patients and no infection developed.

Thromboembolic events were reported in 3 patients in the form of deep vein thrombosis of the lower leg. Deep vein thrombosis developed 3.6 days after the onset of infusion on average. Two of these patients had risk factors for thromboembolic events (one patient had internal malignancy and the other one had a history of a pulmonary embolism). These patients received heparin and warfarin.

Serum IgA levels were measured in 43 patients before the IVIG administration. Among these 43 patients, 3 were IgA deficient. None of these 3 patients had any anaphylactic reactions after the IVIG infusion.

Nausea, vomiting, diarrhea, myalgia, arthralgia, eczema, urticaria, aseptic meningitis, renal failure, anaphylaxis, and death related to IVIG infusion were not observed in our patients.

DISCUSSION

The incidence of adverse effects with IVIG therapy varies widely. The adverse events most commonly reported are minor and include headache, nausea, malaise, myalgia, arthralgia, chills, fever, and chest discomfort. Less commonly reported minor adverse effects include fatigue, dyspnea, back pain, diarrhea, urticaria, leukopenia, hemolytic anemia, changes in blood pressure, and tachycardia. Reducing the infusion rate or temporarily stopping the infusion generally relieves these symptoms. Serious adverse events that include aseptic meningitis, thromboembolism, acute renal failure, and anaphylaxis have been less frequently reported.

The most common adverse reaction in our study was an increase in blood pressure observed in 22% of the infusions and 25% of the patients. This adverse reaction was significantly more frequent in patients with underlying chronic hypertension. Interestingly, the increase in blood pressure during the IVIG infusion was not reported as a common adverse reaction in any of the previous literature; its incidence was much lower in other studies compared to the current study. The reasons for the high frequency of this adverse event in our
study were not clear. The increase in blood pressure in the current study patients was easily treated by reducing the infusion rate in most patients. Antihypertensive drugs were administered to a few patients. All could complete the IVIG therapy.

The second most frequent adverse effect in our patients was fatigue and generalized weakness, seen in 5.3% of the infusions. Its incidence in the current study was comparable with the results of a number of previous studies. The occurrence of other minor adverse effects that included fever, chills, chest discomfort, tachycardia, dizziness, and flushing were low in this and other studies.

We did not observe any anaphylactic reactions to IVIG. These have been rarely reported in the literature. Anaphylactic reactions usually occur in IgA deficient patients who have detectable serum anti-IgA antibodies. We had 3 IgA deficient patients in our series but they received IVIG without any anaphylactic reactions.

Arterial and venous thrombotic events that include stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism have been reported with an incidence of 0.6%-3% per patient and 0.15%-1.2% per treatment course. The exact mechanism of thromboembolic events associated with IVIG is unclear. Serum hyperviscosity caused by the IVIG infusion has been suggested to contribute to the occurrence of thromboembolic events. Three patients in our study developed deep vein thrombosis during the IVIG infusion, of which two had risk factors for thrombosis. It was reasonable that patients with a higher risk of thromboembolic events were infused with a low osmolarity product at a slow rate to reduce the likelihood of thromboembolic events.

The results of our study have shown that IVIG is safe with a few easily manageable minor adverse effects and a very low incidence of serious adverse effects, which is similar to those observed in previous studies. However, knowledge of the adverse effect profile is important. Before considering the use of IVIG in any patient, it is advisable that physicians thoroughly evaluate the patients for possible risk factors for serious adverse effects of the IVIG. Consideration and close monitoring of patients with identified risk factors during the infusion is critical.

REFERENCES


