Adverse reactions of intravenous immunoglobulin

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ABSTRACT

Objective: To study the frequency, type, and severity of adverse reactions to intravenous immunoglobulin infusions and possible preventable measures.

Methods: We prospectively studied the frequency, type, and severity of adverse reactions in 104 intravenous immunoglobulin infusions (Intraglobin^{TM}F) given to 13 patients suffering from several immunodeficiency and autoimmune diseases over 15 months in King Hussein Medical Center. The severity of the reaction was classified as mild, moderate and severe. Transmission of infections such as human immunodeficiency virus, hepatitis B, and C was monitored.

Results: The total number of reactions documented was 16 out of 104 (14.5%) infusions and all resolved without medical aid. Excluding those reactions in which a predisposing factor was identified, the overall rate was 6%.

Conclusion: This study has shown that the overall reaction rate in patients infused with intravenous immunoglobulin at hospital is low. However, establishment of specialized staff will decrease the adverse reactions considerably. We advise the care-taking staff to elicit the predisposing factors like infection and avoid infusion until antibiotics have been started for 24-48 hours. We found that strict application of manufacturer infusion protocols (Intraglobin^{TM}F) will avoid reactions due to accelerating rate of infusion. Intravenous immunoglobulin is a useful life saving drug. It is safe if all precautions are taken into consideration.

Keywords: Intravenous immunoglobulin, adverse reaction.

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It was not until the discovery of agammaglobulinemia in 1952, that the need for antibody-replacement to prevent life threatening bacterial infection was seriously indicated.[1] Intramuscular injections of pooled human immune serum globulin (IgG) can reduce infection in patients with antibody deficiency.[2,3] However, the injections are usually painful, the IgG is slowly absorbed and its therapeutic effect is significantly reduced by local proteolysis.[1] These drawbacks make intramuscular IgG administration less clinically accessible. It was observed that immunodeficient patients, especially when acutely ill, may experience shock-like episodes, hyperpyrexia and chills.[3] Research made it possible to modify immune serum Immunoglobulin in order to be safely given intravenously. Intravenous immunoglobulin (IVIG) is less painful than intramuscular injections, in addition larger doses can be given and higher serum levels can be achieved immediately.[4] The World Health Organization (WHO) suggested the following criteria for the production of IVIG in an attempt to standardise the various preparations: each batch should be prepared from plasma pooled from at least 1000 donors; it should contain at least 90% intact IgG with a sub class distribution that closely matches that in normal serum; all IgG molecules should retain their biological activity, such as the ability to fix complement, it should be free of vasoactive substances such as prekallikrein activator, Kinins,

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Table 1 - Recognized indications for intravenous immunoglobulin.

Replacement therapy	Primary antibody deficiency X-linked agammaglobulinemia X-linked immunodeficiency with hyper-IgM Common variable immunodeficiency IgG subclass deficiencies with infections Severe combined immunodeficiency (SCID) prior to bone marrow transplantation Failure of B cell engrafment after bone marrow transplantation for SCID
Selected cases of secondary antibody deficiency	Intestinal lymphangiectasia Chronic lymphocytic leukemia and B cell lymphoma with hypogammalgobulinemia Myloma with specific antibody deficiency Low birthweight babies of risk of sepsis Infants and children with HIV infection
Immunomodulatory	Immune thrombocytopenia purpura (ITP) Kawasaki's disease Guillian-Barre syndrome Chronic inflammatory demyelinating neuropathy Acquired hemophilia

Plasmin and preservatives, it should as far as possible be free of aggregates, the preparations should be free of infective agents and other potentially harmful contaminants.[5] The use of IVIG is not limited for patients with antibody deficiency, to the contrary, there are several other recognized indications for IVIG summarized in Table 1.[6]

The mechanisms by which IVIG can benefit the 2 types of indications and the doses of IVIG required are different. Therapy in immune deficient states probably depends on straightforward replacement of missing antibodies.[7] The effective dose is usually 0.4gm/Kg/month. Immunomodulatory doses of IVIG for autoimmune conditions are considerably larger.[1,7-9] A dose of 2gm/kg given stat or equally distributed over 5 days is thought to promote blockage of fragment complement receptors on macrophages (preventing phagocytosis of circulating opsonised platelets) or to provide naturally occurring anti-idiotypic antibodies to neutralize pathogenic autoantibodies.[1,6-12] Adverse effects may be divided into events related to infusion itself, complications consequent on infusing high concentration of Immunoglobulin molecules, and transmission of infections as a result of infusing a blood product.[6] The aim of this study is to survey the incidence, frequency, severity and the type of adverse effects of IVIG administration and possible preventable measures.

Table 2 - Recognized indications of intravenous immunoglubulin infusions in King Hussein Medical Center over 15 months.

Indications	Number of patients	Number of infusions over 15 months
X-linked hypogammaglubulinemia	3	42
Common variable immunodeficiency	1	15
T-/B+SCID*	1	3
T-/B-SID	1	3
Transient hypogammaglobulinemia of infancy	2	21
Hyper IgE syndrome	1	15
Kawasaki syndrome	2	3
Systemic onset JRA**	1	1
Guillian Barre syndrome	1	1

* Severe combined immunodeficiency;
** Juvenile rheumatoid arthritis

Methods. This is a prospective study carried out at King Hussein Medical Centre over 15 months from May 1997 to August 1998.

Patients. Thirteen patients with variable Primary Immunodeficiency (PID) and Auto Immune diseases (AID), (Table 2), who were given 104 infusions were enrolled in the study. Two were females and 11 were males. Their ages ranged from one month to 21 years. Staff involved in IVIG infusions had been trained to elicit, prevent and treat the adverse reactions. In the event of an acute infection IVIG infusion was delayed until antibiotic treatment had been instituted for 24-48 hours.

Methods of infusion. All IVIG infusions were given at hospital. Blood samples for Hepatis B surface Antigen; Hepatitis C virus antibodies, human immunodeficiency virus and liver function tests (LFTs) were taken before the infusion started and tri-monthly throughout the study. The rate of infusion was calculated according to the manufacturing

Table 3 - Severity classification of adverse reactions.

Mild	Moderate	Severe
Headache	Chest pain	Tightness of throat
Vomiting	Wheezing	Severe headache or shaking
Flushing	Severe itching	Severe breathlessness or wheezing
Nausea	Mild symptoms getting worse or recuring	Severe dizziness or fainting
Shivering		Sensation of pressure on chest
Itching		Collapse
Muscle aches		
Anxiety		
Light headed		
Irritable		

recommendations. The IVIG product used was (Intraglobin™F). The dose administered was 400mg/kg/month for PID and 2gm/kg stat or 400mg/kg for 5 days for AID. Reactions were defined before the study started according to the criteria shown in Table 3.[13] Data collected using a protocol detailed the symptoms and the time they lasted, the rate of infusion and predisposing factors.

Results. There were 104 infusions in 13 patients. Reactions occurred in 16 infusions, a rate of 14.5%. The type, frequency and the severity of these reactions are shown in Table 4. All reactions occurred during the infusion, except for muscle ache, which was reported 24 hours after the infusion was completed. All reactions were classified as mild and resolved without medical aid. No treatment was necessary in all reactions apart from decreasing the rate of infusion or temporarily discontinuing, some time mild analgesia was given. Predisposing factors were identified in 12 reactions. Accelerating the rate of infusion beyond that recommended by the manufacturer was demonstrated in 10 reactions while administrating IVIG shortly (less than 24 hours) after antibiotics in patients presented with active infection was seen in 2 reactions. In 4 reactions, predisposing factors were not identified. We observed anxiety and irritability on one occasion, it occurred after the 6th infusion in one of our patients. We failed to identify a predisposing factor and at the same time we were unable to make this patient complete the monthly infusions. Fractionation of the determined monthly dose was suggested. Time is needed to check the cost-effectiveness and usefulness of this modification.

Table 4 - The severity and frequency of the adverse reactions during intravenous immunoglobulin.

Adverse reactions	Severity of adverse reactions	Frequency of adverse reactions
Headache	Mild	8
Flushing	Mild	2
Nausea	Mild	2
Shivering	Mild	1
Irritable	Mild	1
Itching	Mild	0
Muscle aches	Mild	1
Anxiety	Mild	1
Chest pain	Moderate	0
Wheezing	Moderate	0
Severe Itching	Moderate	0
Tightness of throat	Severe	0
Severe headache or shaking	Severe	0
Severe breathlessness or wheezing	Severe	0
Severe dizziness or fainting	severe	0
Sensation of pressure on chest	Severe	0
Collapse	Severe	0

Discussion. This study shows that the incidence of adverse reactions is low. The total number of documented reactions was 16 in 104 infusions. Excluding those reactions in which predisposing factors were identified, the over all rate is 6%.[6] Some predisposing factors were avoidable and we found that care-taking staff should be reminded not to give IVIG when an infection is present.[9] If infection is present, antibiotics should be given for 24-48 before IVIG infusion. We emphasize the importance of maintaining a strict infusion rate according to the manufacturer's recommendation throughout the infusion.[6] The association of IgG anti-IgA antibodies was not studied. These antibodies are not routinely assayed in our laboratory due to technical difficulties. Of the 16 documented reactions, none were serious, and all resolved after adjusting the rate of infusion.[9]

In conclusion, this study has shown that the over all reaction rates in patients infused with IVIG at hospital is low following an organized training of care-taking staff. Intravenous immunoglobulin treatment is safe when the care-taking staff are properly trained to prevent and treat adverse reactions, and provide regular monitoring and follow-up of the patients.[13]

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