

Detection of Complications Following Intravenous Immunoglobulins Infusion in A Cohort of Egyptian Children

Aisha Elmarsafy, Nermeen M Galal^{*}, Shrouk M Abdallah and Ilham Youssry

Department of Pediatrics, Cairo University, Cairo, Egypt

^{*}Corresponding author: Galal NM, Department of Pediatrics, Cairo University, Cairo, Egypt, Tel: +20-2-35676105; E-mail: nermeengal@gmail.com

Received date: January 21, 2015, Accepted date: April 19, 2015, Published date: April 26, 2015

Copyright: © 2015 Elmarsafy et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Intravenous immunoglobulins (IVIG) are scarce biological products that are increasingly used in an expanding variety of disorders. Tolerance to infusions is usually well but adverse events, including serious ones have been reported.

Objectives: The study aimed at detection of adverse events following IVIG infusion in relation to preparation, dosing regimen, duration and infusion hours with identification of patients at risk of developing complications.

Material and Methods: An observational study was conducted on a cohort of 55 patients (birth-18 years) who received 62 infusion sessions for different disease conditions over a period of six months. Monitored clinical evaluation and laboratory assessments were done with follow up 7-10 days following the infusions.

Results: Adverse events occurred in 37.1% of IVIG infusion sessions ranging from mild reactions as skin rash, fever to more severe anaphylactoid ones as serum sickness, anemia and acute renal failure. Infusion rate and the presence of risk factors were strong predicting variables for numerous reactions.

Conclusion: Proper justification for use of IVIG with close monitoring of dosage and infusion rate during administration can avoid some reactions. Weighing benefits against hazards is crucial in high risk patients to minimize complications.

Keywords: Intravenous immunoglobulin; Adverse events; Complications

Introduction

Intravenous immunoglobulins (IVIG) are scarce biological products used in an expanding variety of disorders. Tolerance to infusions is usually well but adverse events, including serious ones have been reported.

IVIG is either used as a replacement or immunomodulatory therapeutic agent. Immunomodulatory actions include; the anti-idiotypic activity, neutralizing the autoimmune disease related idiotypes [1]. IVIG may also reduce immune activity by interacting with Fc receptors on phagocytic cells such as splenic macrophages [2,3]. It may also suppress pathogenic cytokines [4].

There are currently few clinical indications for which IVIG has been licensed by the United States Food and Drug Administration (FDA) [5]. Despite this, IVIG has been used increasingly in off label indications in treatment of many conditions in children.

Adverse reactions are reported in up to 20 percent of all intravenous immune globulin infusions [6]. The majority of adverse reactions are minor and transient; common examples include headache and mild rate-related reactions, such as chills or flushing. However, potentially serious systemic reactions of various types occur in 2 to 6 percent of patients [5].

Possible adverse effects may be divided by organ system or by timing of onset; immediate or delayed. Immediate reactions occur during the infusion, and include rate-related reactions including true IgE-mediated anaphylaxis and reactions related to concurrent infection. Delayed reactions are generally rare and occur hours to days after the infusion, and include neurological (e.g. aseptic meningitis), hematological (e.g. hemolysis, and venous thrombosis) and renal complications (e.g. acute kidney injury). However, some of these, particularly thrombotic events, may also occur during infusions [7].

Objectives: The study aimed at detection of adverse events following IVIG infusion in relation to preparation, dosing regimen, duration and infusion hours with identification of patients at risk of developing complications.

Materials and Methods

Design: A cohort observational study.

Location: Patients were recruited at Neonatal Intensive Care Units, Pediatric Intensive Care Units, general and specialized inpatient wards at Cairo University Children Hospitals over a time period of six months, from April through September, 2013.

Set up: The study included 62 transfusions for different disease conditions in 55 patients.

Inclusion criteria

Any disease condition treated with IVIG infusion from birth to 18 years, both sexes.

The study was approved by the Institutional review board and informed consents were obtained from parents or guardians of children.

Assessment before the infusion

- Taking full history of factors predisposing to complications: medical history (renal problems, diabetes mellitus, hypercoagulable states, immunodeficiency, etc), drug history (e.g. nephrotoxic drugs, previous IVIG infusions and any related complications).
- Admission diagnosis (both provisional and final) and its degree of evidence as an indication for IVIG infusion.
- Reason for choice of IVIG as a treatment modality (lack of alternatives, rapid response or failed other options)
- Thorough clinical examination.

Assessment during and after the infusion

- Preparation formulary: brand, percentage, grams per vial and stabilizer (sugars, amino acids or polyols).
- Dosing regimen: grams per dose, number of doses, infusion hours (both intended and actual).
- Symptoms of adverse events: fever, chills, tremors, sweating, rash, itching, body pains, fasting heart beats, limb swelling and pain, respiratory distress, oliguria, urine discoloration, pallor, disturbed conscious level and seizures during and after the infusion. Onset, course and duration of symptoms are determined in relation to the infusion with specification of measures needed to control the symptoms.
- Laboratory work up:

-Initial complete blood count, blood urea nitrogen, creatinine, sodium and potassium serum levels (routine admission labs taken from patient medical record). Blood grouping was done for all the study population.

-Follow up complete blood count, reticulocytic count; serum blood urea nitrogen, creatinine, sodium and potassium serum levels and urine analysis for all patients were done 24-48 hours after the infusion. Further specific tests were individualized according to the suspected complications e.g. Coomb's test for patients who developed anemia, renal biopsy for a patient who developed impaired kidney functions.

The follow up laboratory assessment was done basically once, with exception of the patients who showed laboratory abnormalities following the infusions, those have been traced with specific labs for variable durations .e.g. urine analysis was repeated for patients who showed microscopic hematuria.

- Follow up 7-10 days afterwards through phone calls and/or a hospital visit for the previous symptoms. Patients who developed specific complications were followed accordingly with the needed tests.

Statistical analysis

Data was analyzed using the Statistical Package for Social Science (SPSS) version 15: the following methods were employed: percentage

distributions, median, range, mean and standard deviation. Student t-test and Mann-Witney test were used to compare quantitative variables, and Chi-square test or Fischer's exact test for comparison of categorical variables. Pearson's correlations were used to explore associations between numerical variables. P values less than 0.05 was considered statistically significant.

Results

General patient characteristics

A total of 55 patients, 37 males (67.3%) and 18 females (32.7%), received 62 IVIG infusions.

Ages ranged from birth to 18 years with a mean of 6.09 and standard deviation (SD) \pm 5.36 years with different diagnostic categories. Infections were the most common indication 37.1% (n=23). Twelve patients, 17 infusions (27.4%) had one or more risk factors for adverse events. The risk factors included nephrotoxic drugs (vancomycin, furosemide or immunosuppressive drugs as azathioprine and cyclosporine), preexisting renal problems (lupus nephritis and impaired kidney functions), known allergies (allergic dermatitis), diabetes mellitus and suspected autoimmune disorders.

Three maltose-stabilized intravenous immunoglobulin products were administered to patients based on availability, labeled as products A, B and C. There were no correlations between product types and incidence of adverse events.

Being a scarce product, the study was concerned with clarification of the basis of its usage as regard the FDA approval of the indication and the rational of its use in comparison to other available treatment modalities. The infusion courses included only 14 (22.6%) FDA approved indications. IVIG was used as a combination therapy to other drugs in 33 (53.2%) infusions.

Adverse events

There were 22 symptoms and 26 laboratory changes of adverse events during IVIG transfusions, with some patients experiencing more than one adverse reaction.

Adverse events were noted to occur most frequently within 1 to 6 h from onset of IVIG infusion (n=9, 39.1%). First hour after infusion onset was the most common timing for symptoms of adverse reactions (n=5, 21.7%). Fever and chills were found to be the most common symptoms to occur during the first hour.

The dosage most commonly associated with adverse reactions was 400-600 mg/kg/dose (n=16, 69.6%), infused over 4-7 hours (n=15, 65.2%).

Symptoms of adverse events and their predicting variables

Mild reactions as fever and chills had statistically significant correlations to actual infusion hours, infusion rate and presence of risk factors. Also skin rash and itching had a statistically significant correlation to actual infusion hours.

As for severe reactions; serum sickness had statistically significant correlations to actual infusion hours and presence of risk factors. Pallor had statistically significant correlations to infusion hours and presence of risk factors, Urine discoloration had statistically significant

correlations to dosage, actual infusion hours, infusion rate and the presence of risk factors.

Correlations were also done between the incidence of complications and the presence or absence of primary immunodeficiency disorders in patient diagnosis. A statistically significant correlations was found with fever and chills (P value=0.009), serum sickness (P value=0.000) and pallor (P value=0.000). No statistically significant correlations were found with sweating and flushing (P value=0.67), skin rash (P value=0.39), itching (P value=0.67) or urine discoloration (P value=0.39). Correlations of the incidence of complications to the presence or absence of infections were also done. All symptoms revealed no statistically significant correlations to infections.

Hemoglobin drop

In our study, 14 out of 62 infusions (22.5%) were followed by a significant hemoglobin drop (ranging from 0.5 to 5.6 g %). Seven out of these infusions (50%) were clinically manifested by significant pallor and three infusions were followed by blood transfusions. The hemoglobin drop was noticed following 4 antibody replacement courses (500 mg/kg/dose), 5 courses for immune-mediated thrombocytopenia and another 5 courses for postoperative sepsis with maximum dosing regimen of (1 g/kg/dose).

On analyzing infusions complicated by significant anemia; blood counts showed a mean hemoglobin of 11.27 ± 2.11 g/dl before the infusion and a mean of 8.79 ± 1.68 g/dl after the infusion with a statistically significant difference (p=0.003). As for infusion related risk factors; statistically significant correlations to dose with a mean of 650 ± 240.99 mg/kg/dose (p=0.000) and infusion rate (p=0.000) with a mean of 4.1 ± 2.55 mg/kg/min.

As for possible patient related risk factors for development of hemoglobin drop; predicting variables showed no statistically significant correlations to age (P=0.32) or gender (p=0.15).

Hemoglobin drop showed a strong correlation to primary immunodeficiency. Autoimmunity or blood group type showed statistical significance as predicting variables only when added to the presence of primary immunodeficiency with increased regression value. Infection showed no statistically significant correlations to hemolysis. As for blood group types of our study patients; that blood group A was the commonest in all infusions (n=28, 45.2%), while blood group AB was the commonest in complicated infusions (n=5, 35.7%). However, blood group type alone showed no statistically significant correlation to hemoglobin drop (p=0.07).

Kidney functions and Urine analysis abnormalities

One patient with primary immunodeficiency developed acute non oliguric renal failure following 2 IVIG replacement courses (3.2%) with renal biopsy showing granulomatous nephritis and residual renal affection.

Five patients showed urine analysis abnormalities following 5 IVIG infusions (8.1%); cases that can be interpreted as possible acute hypersensitivity nephritis. As for infusion related risk factors; a mean dose of 760 ± 230.2 mg/kg/dose with no statistically significant correlation (p=0.15), and a mean infusion rate of 2.38 ± 1.35 mg/kg/min with a statistically significant correlation (p=0.045) to urinary abnormalities. As for patient related risk factors; urinary abnormalities showed statistically significant correlations to preexisting renal insufficiency (p=0.03), nephrotoxic drug

administration (p=0.000), with no statistically significant correlation to age (p=0.98), gender (p=0.601) or pre-infusion creatinine level (p=0.37). A statistically significant difference between creatinine levels before and after infusions was detected (p=0.025) (Table 1).

Study sample characteristics	All infusions n=62 (100 %)	Complicated infusions n =23 (37.1%)
Age		
Birth-28 days	24 (38.7%)	5 (21.7%)
1-23 months	10 (16.1%)	4 (17.4%)
2-5 years	11 (17.7%)	4 (17.4%)
6-9 years	13 (20.9%)	10 (43.5%)
≥ 10 years	4 (6.4%)	0 (0%)
Indications (diagnostic category)		
Infections	23 (37.1%)	6 (26.1%)
Hematological disorders	11 (17.7%)	3 (13%)
Neurological disorders	11 (17.7%)	4 (17.4%)
Other autoimmune disorders	6 (9.7%)	2 (8.7%)
Primary immunodeficiency disorders (PIDs)	5 (8.1%)	4 (17.4%)
PIDs with hematological disorders	4 (6.4%)	4 (17.4%)
Unclear diagnosis	2 (3.2%)	0 (0 %)
Risk factors		
No risk factors	45 (72.5%)	9 (39.1%)
Nephrotoxic drugs	11 (17.7%)	8 (34.8%)
Suspected autoimmune disorders	7 (11.3%)	7 (30.4%)
Preexisting renal problems	6 (9.7%)	5 (21.7%)
Allergy	4 (6.4%)	3 (13%)
Type I diabetes mellitus	2 (3.2%)	2 (8.7%)
Multiple risk factors	10 (16.1%)	9 (39.1%)
One risk factor	7 (11.3%)	5 (21.7%)

Table 1: General characteristics of intravenous immunoglobulin transfusion recipients

Discussion

IVIG infusion related complications have been studied by several authors in different cohorts. Palabrica [8] reported 32% of patients with Kawasaki disease and immunodeficiency disorders that were given IVIG infusions experienced adverse events. Fever was the most common manifestation. Symptoms occurred within 1 to 6 h from onset of infusion. Comparable results were recorded by several other studies as Malbran [9] and Katz [7] (Table 2).

Patient-related factors	r	p value	Infusion-related factors	r	p value
Age	0.231	0.071	Dose	-0.113	0.358
Gender	0.226	0.077	Dosing regimen	0.263*	0.039
Presence of one or more risk factors	0.243*	0.029	Course duration (days)	0.113	0.503
Primary Immunodeficiency	-0.442**	0.000	Infusion hours (actual)	-0.111	0.826
Auto-immunity	0.203	0.113	Infusion hours (intended)	0.116	0.370
Nephrotoxic drugs	0.389**	0.002	Infusion rate	0.112	0.317
Infection	-0.175	0.174	IVIG Preparation	0.376**	0.003
Allergy	0.313*	0.013	Final infusion diagnosis	0.269*	0.035
Pre-existing renal insufficiency	-0.062	0.633	FDA approval	-0.384**	0.002

*Correlation is significant at 0.05 levels (2-tailed)
 **Correlation is significant at 0.01 levels (2-tailed)

Table 2: General incidence of adverse events following IVIG and its correlation to patient-related and infusion-related parameters.

Infections were the most common diagnostic category of all complicated infusions (26.1%) in our cohort; however, high incidence of complications among patients with primary immunodeficiency disorders (PIDs) with suspected autoimmune disorders was noted marking them as a high risk group. Infusions for PIDs represented only 14.5 % of total infusions (9 out of 62 infusions); eight of these infusions (88.9%) were complicated by one or more of serious adverse events.

Similarly Tcheurekdjian [10] recruited sixty-five patients with primary immunodeficiencies who received a total of 447 IVIG infusions over a 6-month period. Four hundred fifty-one adverse reactions were noted, with 17% of infusions associated with an intrainfusion reaction and 41% associated with a post infusion reaction.

Dashti-Khavidaki [11], also reported reaction rate of 7.2%; 216 out of total of 3004 IVIG infusions administered to 99 patients with antibody deficiency over a period of 13 years. The highest proportion of adverse reactions occurred in 44 of 54 common variable immunodeficiency (CVID) patients suggesting that CVID patients could be more susceptible to severe adverse reactions, which could be due to the development of autoantibodies and IgG/anti-IgA antibodies.

Regarding autoimmunity, Sherer [12] reported 20 patients (36%) who had adverse events following IVIG treatment courses among fifty-six patients with various autoimmune diseases who were treated with one to six IVIG courses.

As for hematological complications; Berard [13] reported 4 cases of hemolytic anemia following high dose of IVIG (2gm/ kg/dose) for Kawasaki disease (KD). Daw [14] also reported 16 cases of hemolysis identified over a 2 1/2-year period of approximately 1000 patients receiving IVIG (1.6%). They reported Significant hemolysis may occur after the administration of large doses of IVIG (i.e., >100 grams), non O blood group, positive inflammatory serologic marker present.

Kahwaji [15] also identified non-O blood group recipients and chromatographically-purified IVIG preparations with high titers of anti-A and anti-B antibodies as risk factors.

In our study, 14 out of 62 infusions (22.6%) were complicated by hemoglobin drop ranging from 0.5-5.6 g% with a statistically significant difference in hemoglobin level before and after the infusions (p=0.003). Variable dosing regimens (both replacement and immunomodulatory courses) were given with a mean dose of 650 ± 240.99 mg/kg/dose (p=0.000) and a mean infusion rate of 4.1mg/kg/min ± 2.55 mg/kg/min (p=0.000) with high correlation to primary immunodeficiency alone (p=0.000) and when combined with autoimmunity (p=0.002) or blood group type (p=0.005) making a cumulative effect. Higher frequency was noted with AB blood group with no statistically significant correlation to blood group type alone (p=0.07).

As for renal complications; two infusions given to a combined immunodeficiency patient were complicated by renal impairment. The timing in relation to the transfusion sessions as well as the improvement after transfusions were stopped emphasizes the occurrence of renal complications of a predisposed immunodeficient patient with autoimmune disease and an AB blood group. Fakhori [16] reported that acute renal failure (ARF) was a rare complication of intravenous immunoglobulins (IVIG) with an estimated incidence lower than 1 %. Acute renal failure (ARF) has been reported mainly with sucrose containing IVIG but also with maltose and glucose-containing products.

Levy [17] also reported eight patients who showed deterioration in renal function (6.7%) among an unselected cohort of 119 patients receiving two different preparations of IVIG over 20 months, administering 287 courses of IVIG to for a variety of indications. Two patients showed no renal recovery (1.7%). There was no association between the amount of sucrose in the IVIG and development of renal failure. IVIG (regardless of the sucrose content) was associated with renal impairment irreversible.

Most reported cases of renal impairment were related to the use of sucrose-based intravenous immunoglobulin. However Tanaka [18] reported a case of IVIG induced acute tubulointerstitial nephritis without renal failure in a 4-year-old male patient diagnosed as steroid resistant nephrotic syndrome. The IVIG brand he received did not contain sucrose.

Chacko [19] similarly described patients with lupus nephritis treated with an immunoglobulin preparation containing maltose who developed ARF with histological changes characterized by vacuolization and swelling of renal proximal tubular cells. This case had drawn nephrologists' attention to the potential of maltose-based immunoglobulin in producing renal failure.

With IVIG therapy, all patients should have a basic clinical and laboratory evaluation prior to administration. Increasing awareness about the adverse events is needed with paying special attention to patients with risk factors. Weighing benefits and potential hazards of IVIG therapy is essential in those patients.

More attention should be given to the patients with proved or possible immunodeficiency states. Associated autoimmune disorders in such patients who receive a lifelong antibody replacement therapy make them despite the small dosage, at a high risk for serious adverse events as our study showed.

Infusion setting should include proper adjustment of the infusion rate which is the most evident culprit in the majority of adverse events. Adverse events should be anticipated while closely monitoring the patient for early symptoms and signs to allow proper intervention. Follow up of patients after several days is essential to detect late complications.

References

- Blank M, Bashi T, Shoenfeld Y (2014) Idiotype-specific intravenous immunoglobulin (IVIg) for therapy of autoimmune diseases. *Methods Mol Biol* 1060: 353-361.
- Teeling JL, Jansen-Hendriks T, Kuijpers TW, de Haas M, van de Winkel JG (2001) Therapeutic efficacy of intravenous immunoglobulin preparations depends on the immunoglobulin G dimers: studies in experimental immune thrombocytopenia. *Blood* 98: 1095-1099.
- Anthony RM, Kobayashi T, Wermeling F, Ravetch JV (2011) Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway. *Nature* 475: 110-113.
- Siedlar M, Strach M, Bukowska-Strakova K, Lenart M, Szaflarska A, et al. (2011) Preparations of intravenous immunoglobulins diminish the number and proinflammatory response of CD14+CD16++ monocytes in common variable immunodeficiency (CVID) patients. *Clin Immunol* 139: 122.
- Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, et al. (2006) Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 117: S525-S553.
- Pierce LR, Jain N (2003) Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 17: 241-251.
- Katz U, Achiron A, Sherer Y, Shoenfeld Y (2007) Safety of intravenous immunoglobulin (IVIg) therapy. *Autoimmun Rev* 6: 257-259.
- Palabrica FR, Kwong SL, Padua FR (2013) Adverse events of intravenous immunoglobulin infusions: a ten-year retrospective study. *Asia Pac Allergy* 3: 249-256.
- Malbrán A, Larrauri B, Juri MC, Fernández Romero DS (2013) [Adverse events in 1395 infusions with different intravenous gammaglobulin products]. *Medicina (B Aires)* 73: 433-437.
- Tcheurekdjian H, Martin J, Kobayashai R, Wasserman R, Hostoffer R (2006) Intrafusion and postinfusion adverse events related to intravenous immunoglobulin therapy in immunodeficiency states. *Allergy Asthma Proc* 27: 532-536.
- Dashti-Khavidaki S, Aghamohammadi A, Farshadi F, Movahedi M, Parvaneh N, et al. (2009) Adverse Reactions of Prophylactic Intravenous Immunoglobulin; A 13-Year Experience With 3004 Infusions in Iranian Patients With Primary Immunodeficiency Diseases. *J Investig Allergol Clin Immunol* 19: 139-145.
- Sherer Y, Levy Y, Langevitz P, Rauova L, Fabrizzi F, et al. (2001) Adverse effects of intravenous immunoglobulin therapy in 56 patients with autoimmune diseases. *Pharmacology* 62: 133-137.
- Berard R, Whittmore B, Succimarri R (2012) Hemolytic anemia following intravenous immunoglobulin therapy in patients treated for Kawasaki disease: a report of 4 cases. *Pediatr Rheumatol Online J* 10: 10.
- Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, et al. (2008) Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. *Transfusion* 48:1598.
- Kahwaji J, Barker E, Pepkowitz S, Klapper E, Villicana R, et al. (2009) Acute hemolysis after high-dose intravenous immunoglobulin therapy in highly HLA sensitized patients. *Clin J Am Soc Nephrol* 4: 1993-1997.
- Fakhouri F (2007) [Intravenous immunoglobulins and acute renal failure: mechanism and prevention]. *Rev Med Interne* 28 Spec No.
- Levy JB, Pusey CD (2000) Nephrotoxicity of intravenous immunoglobulin. *QJM* 93: 751-755.
- Tanaka H, Waga S, Tateyama T, Sugimoto K, Kakizaki Y, et al. (1999) Acute tubulointerstitial nephritis following intravenous immunoglobulin therapy in a male infant with minimal-change nephrotic syndrome. *Tohoku J Exp Med* 189: 155-161.
- Chacko B, John GT, Balakrishnan N, Kirubakaran MG, Jacob CK (2006) Osmotic nephropathy resulting from maltose-based intravenous immunoglobulin therapy. *Ren Fail* 28: 193-195.