



Drug Use Evaluation of Human Intravenous Immunoglobulin (IVIG) in a Teaching Hospital in East of Iran

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ABSTRACT

Background: Human intravenous immunoglobulin (IVIG) has been used widely for different indications that only a few of them is now approved by the Food and Drug Administration (FDA) as primary immunodeficiency, idiopathic thrombocytopenic purpura (ITP). Although it has been approved for selected indications, the list of its clinical indications, particularly off-labels, has grown considerably. Unfortunately, many of these conditions, lack sufficient clinical data of efficacy and might not always be appropriate.

Method: It was a cross sectional study performed in Amir-al-momenin teaching hospital affiliated to Zabol University of medical sciences. All hospitalized patients who received IVIG during a 6 month period (autumn and winter 2015) were included in this study. We used predesigned data collection forms for data gathering as patient's demographics, diagnoses, as well as drug related data, such as dose regimen, duration, rate of infusion, any related lab test.

Results: In this study total of 49 patients received IVIG. Only in 25 cases, the mentioned indications were FDA approved (51%). Total of 189 IVIG vials (945 grams) that cost 146,475,000 Tomans (39481 USD) was administered during this study period, of which 560 grams (112 vials) (59.2%) were used for FDA approved indications. From 19 ITP patients only 6 (12.2%) fulfilled the criteria for IVIG therapy. Considering cases of wrong doses and whom were not indicated to receive IVIG therapy, total of (93 vials) 465 grams, that cost 72,075,000 Tomans (19427 USD) were spent irrationally.

Conclusion: We concluded that IVIG was widely used irrationally in our institution and cost of this irrational administration is huge. This fact justifies the need for establishing multidisciplinary supervisory procedure in our hospital.

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Introduction

Human intravenous immunoglobulin (IVIG) preparations are made of pooled human plasma taken from thousands of screened volunteer donors and

contain highly purified polyvalent immunoglobulin G (IgG; >90%) (1). It has been used since 1980 and nowadays is used widely among hematologists and neurologists as well as rheumatology, dermatology, and nephrology subspecialties which increased its utilization dramatically (2). It is now approved by the Food and Drug Administration (FDA) for following indications: primary immunodeficiency, idiopathic thrombocytopenic purpura (ITP), B cell chronic lymphocytic leukemia,

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chronic inflammatory demyelinating polyneuropathy, Kawasaki syndrome, and pediatric HIV infection (3, 4). It is also used in many other types of pathologic conditions and the evidence for these off-label uses is stronger in some cases such as Guillain-Barre syndrome, Hemolytic disease of newborn, Myasthenia gravis (3, 4). Although it has been approved for selected indications, the list of its clinical indications, particularly off-labels, has grown considerably. Unfortunately, many of these conditions, lack sufficient clinical data of efficacy and may not always be appropriate. Apart from which indication, it is used for the stage and severity of the condition also should be considered before initiating IVIG to optimize it (3, 4).

Although it can save patients' lives, it can also cause several serious adverse effects such as acute renal toxicity, hypersensitivity reactions, hemolytic anemia, urticarial rashes, hemolysis, and cytopenia besides it carries the risk of blood transmitted disease like hepatitis C (5). It is also an expensive drug product and its estimated cost per gram is about 155000 Tomans (41.77 USD) that make it the most expensive blood product that always rank among five top highly cost drugs in our hospital.

Considering the burden of inappropriate IVIG administration, we designed this observational cross-sectional study in Amir-al-momenin Hospital in Zabol, east of Iran, to investigate the pattern of its administration to aim of rationalizing IVIG use.

Methods

It was a cross sectional study performed in Amir-al-momenin teaching hospital affiliated to Zabol University of medical sciences. All hospitalized patients who received IVIG during a 6 month period (autumn and winter of 2015) were included in this study. Using pharmacy database patients, who received IVIG during this time period, were identified and related data were extracted by reviewing each patient file separately. We used predesigned data collection forms for data gathering. It consists of data about patient's demographics, diagnoses, admission wards and doctor specialty as well as drug related data, such as dose, regimen, and rate of infusion. We also recorded any related lab test (RBC, hemoglobin, platelet, serum creatinine) (4), interacting drugs (live virus vaccines such as MMR), premedication (if patient received any), adverse reactions and outcome. The investigator also interviewed attending doctors and nurses of each patient for any complementary data. We categorized our identified indications into 3 different categories: A) FDA approved indications as: primary immunodeficiency, Idiopathic thrombocytopenic purpura (ITP), B cell chronic lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, Kawasaki syndrome, and pediatric HIV infection (1, 2). B) Off labeled, but strongly recommended as first line: Guillain-Barre' syndrome (GBS), Hemolytic disease of the newborn (HDN), Myasthenia Gravis (3, 4) and C) not

recommended.

We also used following criteria for initiating IVIG therapy in ITP patients:

In pediatrics:

- Life threatening bleeding (e.g., intracranial hemorrhage)
- Severe mucosal bleeding or suspected internal hemorrhage
- High risk of bleeding complications

In adults:

- Severe bleeding (e.g., intracranial, gastrointestinal) and platelet count < 30000/microL
- New diagnose of ITP and any clinically important bleeding and also patients with platelet count < 20000 or 30000/microL even in the absence of bleeding symptoms (3).

Patients were divided in 2 groups of pediatrics (<15 year old) and adults, and related data of each age group were entered in 18 SPSS software separately. Results were expressed as mean \pm SD or percentage.

Results

A total of 49 patients received IVIG (Intratect® made by Biotest company in Germany, each ml contains 50 mg human normal immunoglobulin purity of at least 96% IgG) during our study period. 45 patients (91.8%) were in pediatric group and the rest of them categorized as adults. Patient demographics are summarized in Table 1. Intravenous immunoglobulin was prescribed for 11 different indications described in details in Table 2. In 25 patients (51%) IVIG was used for indication which were approved by FDA and other (49%) mentioned indications were not FDA approved.

A total of 189 IVIG vials (945 grams) that cost 146,475,000 Tomans (39481 USD) was administered during this study period, of which 560 grams (59.2% vials) were used for FDA approved indications. We observed that about 13,950,000 Tomans (3760 USD) were spent for not approved indications (group C) and about 45,725,000 Tomans (12324 USD) for off labeled but strongly recommended as first line indications (group B).

From 19 ITP patients only 6 (12.2%) (5 children and 1 adult) fulfilled the criteria for IVIG therapy (3).

We observed that in 25 patients (51%) who were categorized as group A and B, the ordered IVIG doses were as recommended. While in 14 patients (28.6%) the dose exceeded the recommended and in 2 cases (4.1%) it was less than recommended.

Considering cases of wrong dose and whom were not suitable candidate of IVIG therapy total of 93 vials (465 grams), that cost 72,075,000 Tomans (19427 USD) were spent inappropriately.

Among different wards of our hospital, the Neonatal Unit ranked first in case of IVIG administration (38.8%). The

Table 1. Demographic characteristics of study population.

		Adults	Children
Number of Patient		4 (8.16%)	45 (91.84%)
Gender	Female	3 (6.12%)	22 (44.90%)
	Male	1 (2.04 %)	23 (46.93%)
Median Weight (Kg)		65	6.57
Age	< 40 y.o	2 (4.08%)	< 1 y.o 36 (73.46%)
			1-5 y.o 5 (10.20%)
	> 40 y.o	2 (4.08%)	5-15 y.o 4 (8.16%)

percentage of IVIG administered in different wards of the hospital was as follows: Internal medicine (2%), neonatal intensive care unit (16.3%), intensive care unit (ICU) (10.2%), gynecology (2%) and pediatricians (30.6%). The specialties of prescribers are summarized in Table 3. Furthermore, 47 patients (95.9%) received this drug for the first time while other patients had a previous history of IVIG administration.

The infusion rate was specified in patient files by doctors in 47 (96%) of patients and only in 2 adult patients it was not determined by doctor's order. The lowest rate of infusion was 0.16 ml/kg/h and the highest rate was 7.40 ml/kg/h with a mean of 3.33 ml/kg/h. An ordered infusion rate exceeded upper recommended range by the manufacture (1.9 ml/kg/h) in 33 (67.3%) cases and it was less than recommended in 11 patients (22.4%).

We observed that all of study patients (100%) took just one treatment cycle of IVIG. Length of treatment course varies between 1 and 6 days, with an average length of treatment of 2.24 days.

Two cases of adverse drug reactions reported to IVIG

administration, one case experienced chest tightness and agitation and the other one complained of paresthesia, chest pain and dyspnea. In both cases the infusion rate exceeded the manufacture recommended rate. Infusion of IVIG was stopped in both patients and they were managed by oxygen therapy.

Regarding past medical history, we observed that one patient had history of rheumatoid arthritis, hypertension, and diabetes mellitus. One had a history of hypothyroidism and 5 patients had a history of thrombocytopenia.

There is a potential drug interaction between IVIG and live attenuated vaccines. Considering the national vaccination program (MMR at 12 and 18 months & polio vaccine in 0, 2,4,6,18 months and 6 years) and date of IVIG administration (within 6 weeks of vaccination) (6), we discovered 33 (67.3%) cases of potential drug interaction with polio vaccine and 1 (2%) with MMR (total 34 (69.4%)) in our study population.

Unfortunately 5 patients expired during treatment course and one was sent to more equipped hospital for further therapeutic management and others (43 cases)

Table 2. Indications of Intravenous Immunoglobulin (IVIG) administration.

Indications	FDA approved (a)	off labeled but strongly recommended as first line (b)	Not recommended (c)	Frequency (%)
Idiopathic thrombocytopenic purpura (ITP)	a			19 (38.77)
Primary immunodeficiency	a			2 (4.08)
Kawasaki syndrome	a			4 (8.16)
Guillain-Barre syndrome		b		1 (2.04)
Hemolytic disease of newborn		b		15 (30.61)
Myasthenia gravis		b		1 (2.04)
Pneumonia			c	2 (4.08)
Sepsis			c	2 (4.08)
Influenza			c	1 (2.04)
Fever, Seizure, Meningitis			c	1 (2.04)
Acute Rheumatic Fever			c	1 (2.04)
Total	25 (51.02)	17 (34.69)	7 (14.28)	49 (100)

Table 3. Prescriber specialty/subspecialty.

Doctors specialty/ subspecialty	Number (percent)
Pediatrician	24 (49/0)
Pediatric neurologist	1 (2.0)
Neonatologist	11 (22.4)
Pediatrics infectious disease	9 (18.4)
Internist	3 (6.1)
Neurologists	1 (2.0)

were discharged after symptom improvement.

All the mentioned treatment monitoring parameters; baseline serum creatinine, hemoglobin, platelet and RBC count were measured at 21 (42.8%) patients. Baseline platelet, hemoglobin and RBC count were measured at 77.5% of patients with 34.2%, 44.7% and 64.9% of normal values respectively. Baseline creatinine were measured in 40.8% of patients and 85% of cases were within normal range.

Discussion

Intravenous immunoglobulin is an essential blood product that is used for treatment of different pathologic conditions. The rate of IVIG demand has increased recently. As IVIG is an expensive blood product, policies have been developed to monitor and control the administration process of IVIG in many institutions or countries (7, 8). At our institution IVIG is dispensed just based on a physician's order and there is no other regulatory supervision of pharmacy or any other advisory service on its administration. So it was not surprising that in comparison with other studies, the frequency of cases in which IVIG was used inappropriately is unacceptably high that can lead to a huge waste of money.

The frequency of FDA approved indications in our study was about 51%, while in a similar study performed in 2013 in the US in 33 patients the rate of FDA approved indication was more than ours (73%). On the other hand, at a utilization review of intravenous immunoglobulin in a tertiary care hospital in United Arab Emirates performed from March 2010 to April 2011, in 134 patients (74 adults and 60 children), 57.5% of cases treated for non-recommended indication (9).

Among different FDA approved indications, ITP was the most prevalent diagnoses in our patients. Apart from the fact that some of these thrombocytopenic patients may not be true ITP, based on recent guideline (3) all ITP patients are not suitable candidate of IVIG therapy. Considering other determinants of commencing IVIG therapy in these patients; as platelet count, sign and symptoms of bleeding, neurologic symptoms and ... (as described in the method section in details), from 17 pediatric patients diagnosed with ITP only 5 (10.2%)

patients and from 2 adults only 1 (2.04%) patient, fulfilled the criteria for IVIG therapy. That lowers rate of approved indications even less (24.5%).

The frequency of, off labeled, but strongly recommended as first line indications like Guillain-Barre syndrome, Hemolytic disease of newborn, Myasthenia Gravis was 34.7% in our study, that is about a similar study performed on IVIG utilization at King Khalid University Hospital, over a 3-year period in 2005. A total of 305 patients was identified and IVIG was given to 29 (9.5%) patients for off-label recommended as first line indications in that study (8).

Considering the fact that the dose of IVIG should be calculated based on patient body weight. We observed that a patient's weight was recorded in 95.9 cases. We assumed that in all these cases patient's weight was used for dose calculation. In a similar study by the University of Mississippi Medical Center, in 2011, doses were ordered based on Actual Body Weight in 85% of 25 adult patients (10).

We observed that in about half of our study population the administered dose and drug regimen were as recommended and in 14 (28.6%) of cases it was more than recommended while in 4.1% of patients it was lower. Patients who were categorized as group C were excluded here, as there was no recommended dose for this unapproved indication. Both over treatment and under treatment may lead to undesirable therapeutic consequences. On one hand over treatment can cause adverse drug reactions, increase treatment cost and on the other hand under treatment may lead to therapeutic failure.

In October 2010, a pharmacist-driven stewardship program was implemented at the Brigham and Women's Hospital to ensure continued adherence to the prescribing guideline, focusing on indications for intravenous immune globulin (IVIG) use and dosing per ideal body weight. Total number of patients was 418. Nine patients (2.2%) and two patients (0.5%), respectively, received a different dose or frequency per the prescribed indication (8).

Some IVIG adverse effects may be related to the rate of infusion as fever, flushing, flu-like myalgia, arthralgia, malaise, nausea, vomiting, and headache (7). So it is

important to follow the recommended instruction for infusion by the manufacture. We observed that in 47 patients (96%) the rate of infusion was defined by the doctor. This rate was higher compared to a similar study performed at the University of Mississippi Medical Center, that the infusion rate was specified in 72% of doctors' orders (10). But we observed that the ordered rate of infusion was more than recommended in drug package insert in 33 (67.3%) of cases. This reflects the fact that although doctors are aware about the importance of specifying IVIG administration details, but they are not familiar with different brands of drugs and the importance of following manufacturer's instructions for drug administration. The median rate of infusion in our study was 3.33 ml/kg/h, this rate was lower compared to a similar study performed in 2014 in Iran, which the median infusion rate was 6 ml/kg/h (12).

Based on drug package insert, IVIG administration in 6 to 12 weeks of live attenuated vaccines like MMR can decrease vaccine efficacy so in some cases (e.g. measles) detecting antibody levels are recommended. In case of oral polio vaccine (live attenuated) that is used for national vaccination in Iran this theoretical interaction should also be considered although there is not sufficient data and further study is necessary.

One of the main goals of drug use evaluation studies is decreasing direct and indirect drug cost related to irrational drug administration. In this study, we observed that the total cost of IVIG was 146, 475,000 Tomans (39481 USD), that's about 72,075,000 Tomans (19,427 USD) of this amount was the cost of IVIG administration for either incorrect indications or incorrect drug regimen. In United Arab Emirates, IVIG for inappropriate indications costs more than half of the amount of IVIG dispensed, with a total cost of nearly US\$0.7 million (9).

In conclusion, we observed that IVIG was widely used

inappropriately in our institution and related cost of these inappropriate administrations is huge. This fact justifies the need for establishing multidisciplinary supervisory guidelines for IVIG administration in our hospital as well as periodic follow up.

References

- Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol.* 2013;13(3):176-89.
- Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol* 2010;125(6): 1354-1360.e4.
- Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol* 2017;139(3S):S1-S46.
- Yang L, Wu EY, Tarrant TK. Immune Gamma Globulin Therapeutic Indications in Immune Deficiency and Autoimmunity. *Curr Allergy Asthma Rep.* 2016;16(8):55.
- Ammann EM, Haskins CB, Fillman KM, et al. Intravenous immune globulin and thromboembolic adverse events: A systematic review and meta-analysis of RCTs. *Am J Hematol* 2016 ;91(6):594-605.
- National Center for Immunization and Respiratory Diseases. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60(2):1-64.
- Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med* 2012;367(21):2015-25.
- Rocchio MA, Schurr JW, Hussey AP, Szumita PM. Intravenous Immune Globulin Stewardship Program at a Tertiary Academic Medical Center. *Ann Pharmacother* 2017;51(2):135-139
- Dawoud T, Tatari H, Gebran N. A utilization review of intravenous immunoglobulin in a tertiary care hospital in United Arab Emirates. *European Journal of Hospital Pharmacy: Science and Practice* 2012;19(3):286-8.
- The University of Mississippi Medical Center, The University of Mississippi Health Care, Pharmacy and Therapeutics Committee, Medication Use Evaluation, June 2012.
- Alangari AA, Abutaleb MH, Albarraq AA, Al-Dhowailie AA. Intravenous immunoglobulin utilization in a tertiary care teaching hospital in Saudi Arabia. *Saudi Med J* 2008;29(7):975-9.
- Sohrevardi S, Shafiei A, Mirzania S. Intravenous Immunoglobulin: A Drug Utilization Review at Shahid Sadoughi Hospital in Yazd. *J Pharm Care* 2015;2(4):170-6.