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Evaluation of intravenous immunoglobulin usage pattern in an educational hospital: a descriptive-cross sectional study in Bandar Abbas, IRAN

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Abstract

The goal of drug utilization evaluation (DUE) is to improve patients' care. Studying the administration and utilization pattern of Intravenous Immunoglobulin (IVIg) is an important research topic due to its significant role in the treatment and control of many disorders, its high cost, and limited availability. We aimed to evaluate the pattern of IVIg use in an educational hospital. In this descriptive-cross sectional study, 250 patients' records including medical orders, nursing notes and drug chart were evaluated. We used Food and Drug Administration (FDA) and United Kindom (UK) protocols to evaluate IVIg indications in our study. Data were analyzed using the SPSS software. Prescription of IVIg in our hospital adhered to FDA-approved and UK highly evidence based indications in 64.1% and 67.6% of the cases, respectively. Immune thrombocytopenic purpura (ITP) was the most common indication that IVIg was correctly prescribed for 52.7% based on FDA guideline and 50% based on UK guideline. Sepsis (15.5%), hyperbillirubinemia (10.4%), encephalitis (3.5%), and aplastic anemia (1.38%) were incorrect indications of IVIg in our study. Adverse drug reactions (ADRs) were observed in 14.5% of patients. Consumption of IVIg in our hospital, was more consistent with international guidelines compared to other hospitals in Iran, however unnecessary prescriptions cannot be ignored. We suggest developing national guidelines and educating our prescribers for the use of IVIg to minimize irrational prescription of expensive and important medicines such as IVIg.

Keywords: Drug Utilization Evaluation, Intravenous Immunoglobulin, Inpatient

1. Introduction

Irrational prescription of drugs is a challenge for health care systems, all over the world (1, 2). Optimization of drug prescription, not only leads to reduction in costs, but also, improves quality of treatment and patients' safety (3).

Drug utilization evaluation (DUE) has been introduced in USA and Europe in late 1960s, and is still a major issue in medical research. DUE helps us to investigate drug usage pattern and correct it based on standard guidelines, if necessary (1).

Intravenous immunoglobulin (IVIg) is an expensive biologic product with a difficult process of production. Plasma of many people is required to produce it (4). IVIg is used in immunocompromised patients to protect them against patho-

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gens. Also, it is prescribed in many autoimmune disorders because of immunomodulatory and anti-inflammatory effects (5). The indications of IVIg administration are very different and includ labelled, off-label and investigational use without confirmed clinical evidence (6). So, it is important to optimize consumption of IVIg and save it for patients at real risk. This study aimed to evaluate IVIg usage pattern in an educational pediatric hospital and compare it with two international guidelines.

2. Materials and Methods

This descriptive-cross sectional study was carried out at a Pediatric Hospital, Bandar Abbas, Iran, from September 2017 to February 2018 to investigate the pattern of administration and utilization of IVIg (Privigen®, manufactured by CSL Behring Pharmaceutical Company). The Pediatric Hospital is a Hormozgan University of Medical Sciences (HUMS) affiliated hospital and it is a referral center for pediatric diseases. This study has been approved by ethical committee of HUMS (code: REC.1396.94).

Related information was gathered from hospital Information technology (IT) unit and medical records department, by a Pharm D student. All patients' records including medical history, physician's orders, nursing notes, and medical consulting sheets were studied. Demographic data (age and sex) and weight, the reason for IVIg prescription, adverse drug reactions (ADRs) related to IVIg prescription, medical specialization and the amount of IVIg consumed, were recorded.

We used Food and Drug Administration (FDA) and United Kindom (UK) protocol to evaluate IVIg indications in our study. In the FDA protocol, IVIg indications are classified into approved and non-approved (6). Indications of IVIg graded by coloring in UK protocol, which is defined as 4 colors; Red: highly evidence based, treatment with IVIg considered vital, highest priority, Blue: reasonable evidence based, use of IVIg should be modified in times of shortage, moderate priority, Gray: weakly evidence based, treatment should be planed case by case, latest priority and black: use of IVIg is not recommended (7).

Data were analyzed using IBM SPSS software version 24.0. The Mean ± SD for continuous variables and number (percentages) for descriptive assessment were reported.

3. Results

Among 144 patients' records evaluated in this study, 59.7 % boys and 40.3 % were girls. Patient's age ranged from 1 day to 12 years old. IVIg was ordered for 11 indications: immune thrombocytopenic purpura (ITP)(33.3%), sepsis (15.3%) Kawasaki syndrome (13.1%), hyperbilirubinemia (10.4%), ataxia telangiectasia (9.0%), primary immunodeficiency (6.2%), encephalitis(3.5%), Guillan Barre syndrome (2.8%), allergic skin reaction(2.1%), secondary immunodeficiency (1.4%), aplastic anemia (1.4%) and unknown reasons (1.4%).

The highest and lowest rate of IVIg prescription was related to the hematology oncology ward (23.6%) and Neonatal Intensive Care Unit (NICU) (2.1%), respectively.

Prescription of IVIg in the hospital adhered to labelled indications of FDA with 64.1% and red indications of UK guideline with 67.6%. ITP was the most common cause of the correct prescriptions (52.7% based on FDA guideline and 50% based on UK guideline). In this study, platelet count in ITP patients (n=48) was the following; 10 patients with platelet count <10,000 mm^3, 10 patients with platelet count 10,000-20,000 mm^3, 8 patients with platelet count 20,000-30,000 mm^3, 15 patients with platelet count >30,000 mm^3 and 5 patients did not have complete blood count (CBC) test.

Twenty one (14.5%) patients experienced ADRs related to IVIg infusion. Fever (5.5%), nausea and vomiting (4.2%), headache (2%), hypotension (1.4%), chills and fever (0.7%) and bradycardia (0.7%) were reported. A total of 2,112.5 grams of IVIg with a mean of 14 grams for each patient was administered.

4. Discussion

IVIg is an expensive pharmaceutical product with a difficult process of production and limited access (8). It is used in immunocompromised patients to protect them against pathogens. Also, it is prescribed in many autoimmune disorders be-

Table 1. Patients' demographics and details of IVIg prescriptions.

Variable	Results
Patients' demographics	
Age	1 day – 12 years old
Sex(n)	86 boys and 58 girls
Weight	1500 g- 65 kg
Details of IVIg prescriptions	
Hospital ward IVIg prescribed (percent)	Oncology and Hematology (23.6) Pediatrics (21.5) Neonatal (16.1) PICU (16.1) Surgery (11.1) NICU (9.7)
Medical specialization (percent)	Hematology and oncology (31.9) Infectious (23.6) Pediatrics(20.8) Immunology (15.3) Neurology(4.2) Nephrology (1.38) Gastroenterology(1.38) Pulmonology (1.38)
Cause of IVIg administration (percent)	ITP (33.3) Sepsis (15.3) Kawasaki (13.1) Hyperbilirubinemia (10.4) Ataxia-telangiectasia (9.0) Primary immunodeficiency (6.2) Encephalitis (3.5) Guillan barre (2.8) Allergic skin reaction (2.1) Secondary immunodeficiency (1.4) Aplastic anemia (1.4) Unknown (1.4)
Consumed IVIg (gr)	2,112.5 g
Adherence to FDA guideline (percent)	FDA app (64.1) FDA non- APP (35.9)
Adherence to UK guideline (percent)	Red (67.6) Gray (15.5) Black (15.5) Blue (1.4)
ADRs(percent)	Fever (5.5) Nausea and vomiting (4.2) Headache (2) Hypotension (1.4) Chills and fever (0.7) Bradycardia (0.7)

IVIg: Intravenous Immunoglobulin, g: gram, Kg: kilograms, PICU: Pediatric intensive care unit, NICU: Neonatal Intensive Care Unit, ITP: Idiopathic Thrombocytopenic Purpura, FDA: Food and Drug Administration, UK: United Kingdom, ADRs: Adverse Drug Reactions.

cause of immunmodulatory and anti-inflammatory effects (6, 8, 9). The use of IVIg in many off-label or non-approved indications is a dilemma, and it still is prescribed in various disorders without any

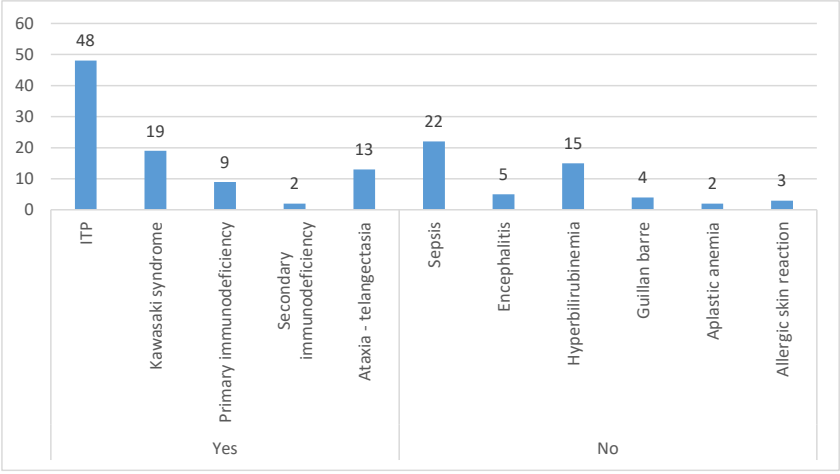

Figure 1. Indications for IVIg administration based on FDA guideline.

confirmed clinical evidence. DUE helps us to investigate drug usage pattern and correct it based on standard guidelines, if necessary (2, 3).

The present study was designed to assess the pattern of consumption of IVIg in an educational pediatric hospital in Bandar Abbas and compare it with international guidelines. All the previous studies just used FDA guideline as a standard; we decided to add UK guideline as a second standard (4, 10, 12).

We found that 33.3% of the patients received IVIg related to ITP that was consistent with the result of previous researches in Iran (4, 10). although, Rezaei *et al*. reported that neurological disorders were the most common reason for IVIg prescription in a teaching hospital (13).

Treatment of ITP with IVIg is FDA approved and one of the red indication of UK guideline, but prednisolone is considered the first treatment choice (10). Since, a number of studies have shown benefits of IVIg in treatment of ITP, it is prescribed in most patients as the first line (14, 15). However, prednisolone is cheaper, easier to administer and more accessible (16).

Increasing platelet counts and reducing the risk of bleeding is the goal of therapy in ITP (16). Based on British Hematology Society, the use of IVIg in ITP should be allocated to cases with acute risk of bleeding (17). Also, American Hematology Association recommends treatment with IVIg or corticosteroids in pediatrics whose platelets are less than 20,000 mm^3 and have mucus bleeding as well as those whose platelets are less than 10,000 mm^3. In pediatrics with platelet count above 30,000 mm^3, no treatment is required and only follow up is recommended (18). In this study,

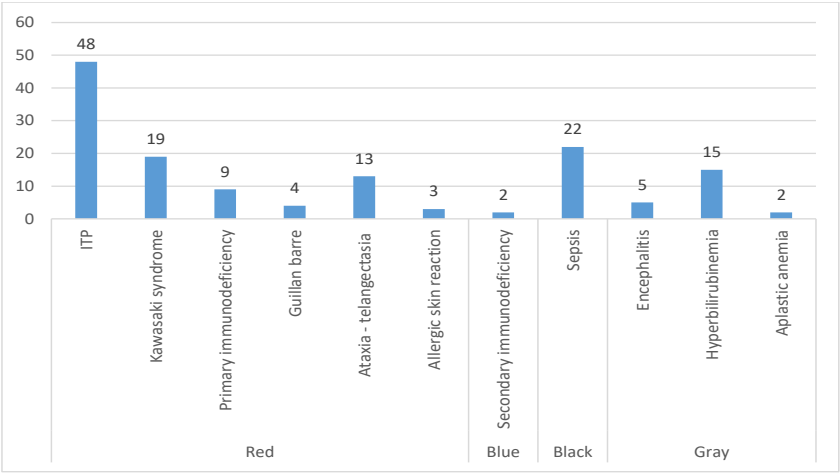

Figure 2. Indications for IVIg administration based on UK guideline.

20 patients had platelet count <20,000 mm^3 with no history of bleeding. Fifteen patients with platelets>30,000 mm^3 were reported. Closer assessment of these patients, reveled two points: first, they had a long history of inpatients visit because of ITP, and second they showed a sudden platelet drop in their CBC test.

Other indications of IVIg in our study, were: sepsis (15.3%), Kawasaki syndrome (13.1%), hyperbilirubinemia (10.4%), ataxia-telangiectasia (9%), primary immunodeficiency (6.2%), encephalitis (3.5%), Guillan barre (2.8%), allergic skin reaction (2.1%), secondary immunodeficiency (1.4%) and aplastic anemia (1.4%). In two patients (1.4%), the exact cause of IVIg prescription was not specified (Table 1). Incomplete patients' records was our main challenge in this retrospective study.

Based on above data, prescription of IVIg in our hospital adhered to FDA-approved indications and red indications of UK guideline with 64.1% and 67.6%, respectively (Figure 1 and Figure 2). Both guidelines, agree on the following disease; ITP, primary immunodeficiency, Kawasaki syndrome, sepsis, encephalitis, aplastic anemia and hemolytic disease of newborn, but UK guideline recommends prescription of IVIg for Guillain-Barre syndrome and allergic skin reaction (Toxic epidermal necrolysis, Stevens Johnson syndrome) unlike FDA guideline (7).

Twenty-one (14.5%) of all patients (n=144) experienced adverse drug reactions related to IVIg infusion. Fever (5.5%), recorded more often that was compatible with other publications (4,10). Also, patients complained of chills and fever (0.7%), nausea and vomiting (4.2%), headache (2%), hypotension (1.4%) and bradycardia (0.7%) in our research. High infusion rate, change of brand used and patient's sensitivity are among factors which contribute to these complications (10). We don't have generic form of IVIg in Iran and a commercial product may not be available at all times, but we can prevent ADRs by controlly infusion rate of IVIg; starting with low rate and increasing gradually. However, patients receiving IVIg for the first time are more susceptible to complications of injections.

It is the first study used a European guideline (UK) as a second standard and compared with FDA guideline. But, our study was accompanied by several limitations: low sample size, incomplete patient's medical records, and failure to report IVIg administration pattern and no discussion about direct cost. We have performed a retrospective, observational study and assessed IVIg use pattern with no intervention. It is better to compare IVIg consumption before and after an intervention, as Karimzadeh et al. pharmaceutical care team in Namazi Hospital, Shiraz, observed guideline implementation for high cost medications, such as intravenous pantoprazole and albumin, decreased the total amount of administered medications and their relative cost by 50.76%. Although, they could not prove this intervention, was effective for IVIg (19).

5. Conclusion

Our result is more correlated with FDA guideline than reported by others, in Iran. Of course unnecessary prescriptions cannot be ignored (4, 10). For the first time, a European guideline was also used alongside the American Guideline. It is recommended more research with longer duration of study and larger sample size to be done. In addition, more interventional studies about high cost dtug such as IVIg, help us to create national guidelines.

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Conflict of Interest

None declared.

6. References

1. Doherty P, Kirsa S, Chao S, Wiltshire S, McKnight D, Maxwell D, et al. SHPA Standards of Practice for Drug Use Evaluation in Australian Hospitals. *J Pharm Pract Res.* 2004;34(3):220-3
2. Phillips MS, Gayman JE, Todd MW.

ASHP guidelines on medication-use evaluation. American Society of Health-system Pharmacists. *Am J Health Syst Pharm.* 1996;53(16):1953-5.
3. WHO Drug and Therapeutics Committee Training Course - Participant's guide. Available at: www.who.int/medicines/technical_briefing/tbs/Participant-s-Guide- All-Sessions. Accessed 2007.
4. 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.
5. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol*. 2005;142(1):1-11.
6. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. doi: 10.1016/j.jaci.2016.09.023.
7. Clinical Guidelines for Immunoglobulin Use implemented in 2008 - Gov.uk. available at: https://www.gov.uk/ government/publications/clinical-guidelines-for-immunoglobulin-use-second-edition-update. Accessed august 20, 2011.
8. Prasad A N, Chaudhary S. Intravenous immunoglobulin in pediatrics: A review. *Med J Armed Forces India.* 2014;70(3):277-80. doi: 10.1016/j.mjafi.2013.05.011.
9. Lemieux R, Bazin R, Néron S. Therapeutic intravenous immunoglobulin. *Mol Immunol.* 2005;42(7):839-48.
10. Dashti-Khavidaki S, Khalili H, Farshadi F, Aghamohammadi A, Movahedi M, Hajibabaei M. Inpatient pediatric use of intravenous immunoglobulin at an academic medical centre. *Singapore Med J.* 2008;49(2):147-9.
11. Chen C, Danekas L H, Ratko T A, Vlasses P. A Multicenter Drug Use Surveillance of Intravenous Immunoglobulin Utilization in US Academic Health Centers. *Ann Pharmacother.* 2000 Mar;34(3):295-9.
12. Galal NM. Pattern of intravenous immunoglobulins (IVIG) use in a pediatric intensive care facility in a resource limited setting. *Afr Health Sci.* 2013;13(2):261-265. doi:10.4314/ahs.v13i2.9
13. Rezaie N, Shajareh E, Motamed MR, Ghanbari B, Pakdaman N, Farasatinasab M. Intravenous Immunoglobin Utilization Study in a Teaching Hospital. *Arch Iran Med.* 2019;22(5):232-5.
14. Godeau B, Chevret S, Varet B, Lefrere F, Zini JM, Bassompierre F, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet*. 2002 Jan 5;359(9300):23-9.
15. Hedlund-Treutiger I, Henter JI, Elinder G. Randomized study of IVIg and highdose dexamethasone therapy for children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol.* 2003 Feb;25(2):139-44.
16. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. 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.* 2006;117(4 Suppl):S525-53.
17. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol.* 2003 Feb;120(4):574-96.
18. Lu KH, George JN, Vesely SK, Terrell DR. Management of primary immune thrombocytopenia, 2012: A survey of Oklahoma hematologists-oncologists. *Am J Med Sci*. 2013;347(3): 190-4.
19. Vazin A, Karimzadeh I, Karamikhah R, Oveisi Z, Mohseni S, Keykhaee, et al. Clinical and economical impacts of guideline implementation by the pharmaceutical care unit for high cost medications in a referral teaching hospital. *BMC Health Serv Res.* 2018;18(1):815. doi: 10.1186/s12913-018-3627-3.