Advances in Pharmacology and Therapeutics Journal
Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Case Series

Evaluation of Intravenous Immunoglobulin Usage in a Teaching Hospital: A Case Series Study in Kerman, Iran

Running Title: *Intravenous Immunoglobulin* Utilization Evaluation

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ARTICLEINFO

Received: 08/22/2024

Accepted: 10/05/2024

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Abstract

Background: Assessing the utilization of intravenous immunoglobulin (IVIG) is crucial due to its high cost and limited availability. IVIG preparations are utilized in various disorders. This study aimed to investigate the prescribing and consumption patterns of IVIG at Kerman Afzalipour Hospital and to propose strategies for reducing drug expenditures.

Materials and Methods: Over one year, physician orders and patient charts of individuals treated with IVIG were reviewed to collect data. Descriptive statistics were employed for data analysis using SPSS software.

Results: During the study period, 62 IVIG administrations were documented at the hospital, with 54.1% involving female patients. Of these, 51.4% were prescribed for labeled indications, while 48.6% were for off-label indications. No contraindications were observed, although precaution was warranted in 9.6% of cases, which was not consistently addressed, and laboratory parameters were not evaluated in any case.

Conclusion: This study reveals that IVIG infusions for off-label indications were nearly as frequent as those for labeled indications.

Keywords: Drug Use Evaluation, Drug Utilization, Intravenous Immunoglobulin, Indications

Citation: Asadipour A, Moharamkhani M, Rashidinejad H, Sohrevardi M. Evaluation of Intravenous Immunoglobulin Usage in a Teaching Hospital: A Case Series Study in Kerman, Iran Adv Pharmacol Ther J. 2024;4(1): 21-26.

Introduction

Drug Utilization Evaluation (DUE) is a systematic quality improvement process that assesses medication use patterns and their consequences (1). It plays a crucial role in enhancing prescription practices, administration procedures, and overall medication utilization within healthcare systems (2). DUE studies typically focus on medications with high costs, scarcity, or specific applications, aiming to optimize clinical effectiveness while managing healthcare system finances (3). Intravenous immunoglobulins (IVIGs) are derived from pooled human plasma and have a wide range of clinical applications (4). Intravenous immunoglobulin (IVIG) products are available in various formulations, including lyophilized powders and liquid forms, with differences in manufacturing processes, excipients, pH, and physicochemical properties affecting their clinical efficacy and tolerability (5). Regulatory bodies and expert panels have issued recommendations to rationalize the use of intravenous immunoglobulin (IVIG) due to its scarcity and cost (6). The FDA has approved IVIG for several conditions, including primary immunodeficiency, idiopathic thrombocytopenic purpura, and Kawasaki disease. However, IVIG is frequently used off-label for various autoimmune and other disorders (6, 7). The University Hospital Consortium Expert Panel developed consensus recommendations for 53 off-label indications, emphasizing that IVIG should be used only when standard approaches have failed or are contraindicated. The panel also recommended considering IVIG products as therapeutically equivalent and interchangeable, while taking into account pharmaceutical differences and patient status when selecting a product (8). These guidelines aim to promote appropriate and efficient use of IVIG in clinical practice.

Given the high cost, growing utilization, complex production, and availability of potentially more cost-effective alternatives evaluating the utilization of IVIG is crucial. This study aimed to investigate the administered dose, reasons for IVIG prescription, and demographic variables of patients receiving IVIG in a teaching hospital in southern Iran.

Methods

The cross-sectional study was conducted at Afzalipoor Teaching Hospital in Kerman, southern Iran, spanning one year from April 2012 to May 2013. This hospital is the largest teaching facility affiliated with Kerman University of Medical Sciences. The study population consisted of patients who received parenteral intravenous immunoglobulin during the specified period.

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The data collection methods involved daily collection of information from the wards where there was a demand for IVIG, obtained from the central pharmacy of the hospital. A specialized form

  DOI:https://doi.org/10.18502/aptj.v4i1.16712

detailing prescription and administration instructions for IVIG was completed for each patient. This form was developed by the Advisory Council on Hospital Formulary System. Information was extracted from patients' documents and records, interviews with attending physicians, and para-clinic data. Statistical analysis was performed using SPSS15, employing descriptive statistics such as frequency and percentage to analyze the gathered data.

Results

During the study period, out of 62 patients who received IVIG, 33 were female and 29 were male. IVIG was administered for four different indications: idiopathic thrombocytopenic purpura (37.8%), Kawasaki disease (8.1%), bacterial infection disease (4.1%), and immunodeficiency disorders (1.4%). Among these cases, 51.4% received IVIG based on FDA approval, while 48.6% were off-label.

Among the 24 cases where IVIG use was not FDA-approved, the most common reason for therapy was in the NICU ward, where IVIG was administered for preterm neonatal sepsis (5 cases) and icter (19 cases). **(Table 1)**

Table 1. The number of patients in each case and the FDA approval status of their IVIG administration.

Indication	Percentage of Patients	Number of Patients	FDA Approval Status
Idiopathic thrombocytopenic purpura (ITP)	37.8%	23	Approved
Kawasaki disease	8.1%	5	Approved
Bacterial infection disease	4.1%	3	Off-label
Immunodeficiency disorders	1.4%	1	Approved

The administered dose varied, with most cases receiving 400-500mg/kg, except for neonatal sepsis and icter where a dose of 1-3.5g was given. The administration period ranged from single administrations to 5-day courses. In 9.6% of cases, precautions were not taken during IVIG administration. Additionally, 1 patient (1.4%) received IVIG despite acute obstruction of the respiratory tract, 4 patients (5.4%) had bacterial infections but received IVIG, and 1 patient (1.4%) received IVIG alongside a nephrotoxic drug without precautions. Physical signs were controlled in 18 patients (24.3%), while they were not controlled in the remaining 75.7%. Furthermore, laboratory parameters were not investigated in any patient during IVIG injection. **(Table 2)**

Table 2. Complications and preventive measures (or lack thereof) associated with IVIG administration.

Observation	Percentage of Cases	Number of Cases
Precautions not taken	9.6%	6
Acute obstruction of the respiratory tract	1.4%	1
Bacterial infections but received IVIG	5.4%	4
IVIG with the nephrotoxic drug without precautions	1.4%	1

Discussion

In this study, we assessed the utilization pattern of IVIG at Afzalipour Hospital, with a particular focus on its use for off-label indications. Drug utilization evaluation (DUE) encompasses a comprehensive evaluation of the medication administration process, aiming to enhance prescription practices, administration procedures, and overall medication

use within healthcare systems. DUE programs play a crucial role in improving clinical outcomes and managing healthcare system finances, often focusing on medications with high costs and usage due to their significant impact on healthcare expenditures and patient care.

IVIG serves as a modulating agent, capable of modulating various immune pathways such as the complement system, suppressing idiopathic antibodies, saturating Fc receptors on macrophages, and inhibiting inflammatory mediators like cytokines, chemokines, and metalloproteinases. However, the production process of IVIG is intricate and expensive. Therefore, IVIG administration should be reserved for cases approved by the FDA or where efficacy has been validated in large-scale studies. In Afzalipour Hospital, out of 62 patients, only 38 (51.4%) received IVIG based on FDA-approved indications.

Neonatal sepsis remains a significant cause of mortality and morbidity among preterm infants. Immunoglobulins have been explored as an adjuvant treatment for managing preterm neonatal sepsis. However, recent meta-analyses have cast doubt on the efficacy of immunotherapy in this context, warranting further well-designed studies to clarify its role. In our study, IVIG was administered in 5 cases of neonatal sepsis, which may not be considered rational use at present.

In cases of infections, IVIG may offer beneficial mechanisms such as enhancing serum bactericidal activity, promoting phagocytosis, and neutralizing bacterial toxins. However, it's important to note that the only FDA-approved indications for IVIG use in infections are for preterm infants or cytomegalovirus infection in transplant recipients. When considering IVIG for infection treatment, factors such as cumulative evidence, cost-effectiveness, and the risk of complications should be carefully weighed.

Another Cochrane review indicated a significant reduction in mortality when IVIG was compared to placebo in cases of sepsis (RR 0.81; 95% CI 0.70–0.93). However, when analyzing trials with a low risk of bias, no mortality reduction was observed (RR 0.97; 95% CI 0.81–1.1).

In the case of immune thrombocytopenic purpura (ITP), IVIG has shown clear benefits compared to steroids. However, its use is reserved for patients who do not achieve immediate remission with steroids and when remission is anticipated, necessitating steroid-sparing agents.

Kawasaki disease, characterized by childhood acute vasculitis, is typically managed with standard therapy comprising high-dose IVIG and aspirin. Initial IVIG therapy typically leads to rapid resolution of clinical symptoms in 80–90% of patients with Kawasaki disease and has been shown to reduce the risk of coronary artery complications. While the precise mechanism of action of IVIG in Kawasaki disease remains unclear, a single dose of 2 g/kg administered over 10–12 hours, along with aspirin within 10 days of fever onset, results in rapid symptom resolution in the majority of patients. Moreover, this treatment regimen has been demonstrated to reduce the risk of coronary artery complications from 20–25% to approximately 2–4%.

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Attention to infusion reactions during IVIG therapy is crucial, as these reactions can range from mild to severe and may include fever, chills, nausea, vomiting, backache, headache, facial redness or flush, dyspnea or shortness of breath, dizziness, hypotension or hypertension. These reactions typically occur within 3 minutes to 1 hour after the start of infusion. The incidence of these complications tends to increase with factors such as the presence of infection, high infusion rates, use of various commercial products, and the patient's first-time infusion.

In this study, IVIG was administered in cases with acute respiratory tract obstruction, concomitant nephrotoxic drug use, and bacterial infections. However, precautions for IVIG administration were not observed, and laboratory parameters were not investigated during IVIG injection. While some studies suggest the effectiveness of IVIG therapy in certain conditions, further research is needed to establish its efficacy and safety. Additionally, the cost-effectiveness of treatment should be taken into consideration.

Conclusion

The rationalization of IVIG use is essential to ensure its availability for patients who truly require it, particularly when effective alternative treatment options are available. Guidelines for IVIG use should be developed based on locally available treatment options, taking into account factors such as efficacy, safety, and cost-effectiveness.

Given the high prices of IVIG, its increasing utilization, and the complex production process involved, along with the availability of potentially more economical alternatives with similar effectiveness, the evaluation of IVIG utilization is necessary. This research underscores the importance of assessing IVIG usage patterns in healthcare settings.

The study revealed that IVIG was not used appropriately in this teaching hospital, highlighting the need for better adherence to guidelines and protocols to optimize IVIG utilization and ensure it is reserved for patients who will benefit the most from its use.

Conflict of Interests: The authors declare no conflict of interest.

Funding: No

Acknowledgments: We thank Zahra Azimi to contribute to publishing this article.

Ethical considerations: No biased point of view based on the conflict of interest and personal bias of the authors has been considered in reviewing the sources and organizing the contents of this article.

Authors and contributions: Ali Asadipour and Hamidreza Rashidinejad to create an idea and let us reach the patient's documents.

Mahdieh Moharamkhani for writing the article and working on it as her pharmacy degree thesis and collecting the data, Seyed Mojtaba Sohrevardi for supervision the study and editing the article.

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