Original Article

Predicting Factors for the Pattern of Intravenous Immunoglobulin Utilization in a Middle Eastern University Hospital

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ABSTRACT

Objective: The dramatic increase in the consumption of intravenous immunoglobulin (IVIG) products in nonapproved indications, its high cost, and the severe shortage has developed the concerns of its irrational utilization, especially in the Middle East countries. Therefore, this clinical study attempts to describe the pattern of IVIG administration in one of the largest hospitals in Iran and find the variables associated with inappropriate IVIG utilization. **Methods:** This cross-sectional medication utilization study was conducted in one of the largest referral hospitals in Iran. Random IVIG administrations were assessed from different wards for 9 months. Different data were collected to evaluate the pattern of IVIG administration and find variables, which could predict this behavior. **Findings:** IVIG was prescribed for approved indications in 72% of 201 patients recruited in our study. Although, the rate of drug administration was appropriate in most of the study population, hydration and pre-medication were unsuitable in more than one-third of the patients. Among the variables analyzed to find the factors affecting the misuse of IVIG, female gender, older age of patients, and longer time to start IVIG administration due to hospital admission were statistically significant in the multivariate model. **Conclusion:** Despite the fact that inappropriate use of IVIG was confirmed in less than 30 % of its utilization for the studied patients, it caused a potential risk of treatment complications and a notable and unjustifiable burden of unnecessary costs for this University hospital.

KEYWORDS: *Drug use evaluation, Food and Drug Administration, intravenous immunoglobulin*

INTRODUCTION

Intravenous immunoglobulin (IVIG) is composed of highly concentrated immunoglobulin G; the main immunoglobulin which exists in human serum.[1] It has been primarily introduced for treating immune deficiencies; however, anti-inflammatory and immunoregulatory properties of IVIG have been considered, over the last decades, for the management of various autoimmune and inflammatory disorders.[2] Based on the available evidence, this rapid expansion of IVIG indications has been led to the increasing employment of IVIG for unapproved indications. However, the narrowed indications were approved in clinical guidelines.[3-6]

For example, the US Food and Drug Administration (FDA) approved only seven official indications for using IVIG, including primary immunoglobulin deficiency (PID), idiopathic thrombocytopenia purpura, Kawasaki disease, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, chronic lymphocytic leukemia, and passive immunity.[1]

It should be noted that strong evidence or experts' opinion also support some of the off-label indications for the use of IVIG, suggesting it is considered

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efficacious.[1,4,7] Although some of these IVIG indications are only supported by limited data, these off-labeled indications are still considered in practice by many consultant and academic physicians.[8] It must be noticed that over 150 unlabeled use of IVIG exceed the FDA labeled indications and attributed for the most IVIG usage with a considerably high cost.[4]

Limited availability, economic burden, and a wide range of IVIG off-labeled indications have emerged challenges for health-care providers with regard to the rational prescribing of IVIG.[9,10] Therefore, specific rules and regulations have been set for monitoring the IVIG usage. The clinical guidelines of IVIG from European Union, Australia, and Canada, are among the best examples of these guidelines and protocols.[11-16]

Several studies have previously been conducted to evaluate the concordance of IVIG usage with the established protocols and guidelines. However, there is still inconsistency in different protocols to categorize the IVIG indications, and it is strongly recommended to organize a local clinical committee in each healthcare institute to review the indications and approve a specific protocol for the use of this highly expensive drug.[17,18]

Consequently, concerns for increasing the rate of IVIG irrational prescribing and associated cost in the world made us to determine the prescribing and administration pattern of IVIG in one of the largest hospitals in the Middle East region and to find the possible factors which can affect the misuse of IVIG.

Methods

This cross-sectional research was carried out at one of the largest hospitals in Iran which are located in Isfahan and is affiliated with Isfahan University of medical sciences during a 9-month period, and the data were collected prospectively. The hospital information system (HIS) was used to find and identify the patients who received IVIG, and 201 patients were randomly recruited to the study from different wards of the hospital based on the proportion of the previous usage of IVIG in these wards.

Demographic characteristics, medical condition which was the reason for prescribing IVIG, dose amount and regimen, rate of administration, pre-medication and hydration status of patients before IVIG administration, related adverse effects and the physicians' sub-specialty were recorded from the medical records and electronic data of the HIS on a daily follow-up basis.

To evaluate the concordance of IVIG indications with the standard and rational prescribing guidelines, we sub-categorized the identified indications of IVIG in to three main categories, in accordance with the Lexicomp IVIG drug information:[19] (a) FDA labeled indications, (b) off-labeled with support (strong evidence suggest its efficacy), and (c) off-labeled with no support (there is not any, or sufficient evidence to justify its usage). In our study, IVIG indications in the categories, A and B were flagged as appropriate, whereas category C indications were considered inappropriate.

Other details and considerations such as the rate of administration, pre-medications, and hydration before IVIG administration were also compared with their standards of care as summarized in Table 1.[20]

Cost of IVIG misuse, patient outcomes, mortality rates, and factors related to IVIG's inappropriate usage was also recorded, and identifiable risks related to prescribing this drug were also reported.

The collected data were analyzed using the 20th version of SPSS statistical computer software (IBM, USA). Frequencies and percentages were used to report the qualitative data, whereas the quantitative results were expressed by the mean and standard error [SE]. The normal distribution of data was confirmed by the Kolmogorov–Smirnov test. Independent sample *t*-test and Chi-squared test were performed to compare the quantitative and qualitative variables between two independent groups, respectively. Furthermore, the one-way analysis of variance (ANOVA) test was used to

Table 1: Standards of intravenous immunoglobulin administration

Different aspects of IVIG administration	Standard of care administration
Premedication	
Acetaminophen	Children: 10-15 mg/kg (maximum 500 mg) orally
	Adult: 650-1000 mg orally
Ibuprofen	Children: 10 mg/kg (maximum 400 mg) orally
	Adult: 400-800 mg orally
Prednisone or prednisolone	Children: 0.5-1 mg/kg (maximum 40 mg)
	Adult: 40-60 mg
Methylprednisolone	Children: 0.5-1 mg/kg (maximum 40 mg) IV
	Adult: 40-60 mg IV
Hydrocortisonesodium succinate	Children: 2 mg/kg IV
	Adult: 100 mg IV
Hydration	Normal saline 10-20 mL/kg (before starting IVIG infusion)
Infusion rates	It is better to start the IVIG infusion with a rate of 0.01 ml/kg/min (0.5-1 mg/kg/min) and was speeded up every 20-30 min while controlling for the patients vital signs

IVIG=Intravenous immunoglobulin, IV=Intravenous

assess the significant differences of continuous variables in more than two different groups and the Kruskal–Wallis test was used to assess these differences when the assumptions of one-way ANOVA were not met for the nonparametric data.

Logistic regression analysis was also used to assess the associations between variables and the misuse of IVIG. Univariate regression analysis verified the importance of each variable, and after that, multiple logistic regression analysis was performed to evaluate the association between the previously significant risk factors and the IVIG misuse. Value of $P \leq 0.05$ was considered statistically significant.

The study protocol conformed with the requirement of the Ethical Committee at Isfahan University of Medical Sciences and approved by its Institutional Board of human studies (registration number: 393649).

Results

A total of 201 patients, who received IVIG during the 9-month period of the study were included and analyzed. They mainly included adults with the mean age of 43.4 ± 1.3 years old, whereas, only 20.9% of patients were children, who had the mean age of 9.7 ± 0.8 years.

IVIG prescribed by neurologists included 48% of the total IVIG prescriptions in our study, followed by clinical immunologists (35%), hematologists (4%), rheumatologists (3.5%), nephrologists (3.5%), dermatologists (2%), infectious disease specialists (2%), and neonatologists (2%).

IVIG was given for 26 different indications in our study and the appropriate indication (categories A and B) represented for 72% of the total IVIG indications. Distribution of IVIG indications among the three main categories and the number of patients received IVIG for certain indications were given in detail in Table 2.

The mean dose of prescribed IVIG during the treatment cycle of the study was 0.43 ± 0.14 mg/kg, and the Kruskal–Wallis test showed that this value was significantly higher in ICU patients than other patients ($P = 0.004$).

All the variables were analyzed to identify and evaluate the potential factors affecting the misuse of IVIG. According to univariate analysis, a significant increase in the risk of IVIG misuse had been observed in the older population and female patients ($P < 0.001$). Hospital ward admission was also a major predictor of IVIG misuse in univariate analysis. Furthermore, this analysis showed administration of IVIG in the day clinic was more appropriate than other wards ($P < 0.001$).

Table 2: Distribution of patients based on the category of intravenous immunoglobulin administration

Category of indication	Number of patients (%)
Category A	105 (52.2)
Primary humoral immunodeficiency disorders	51 (25.4)
Chronic inflammatory demyelinating polyneuropathy	43 (21.4)
Idiopathic thrombocytopenic purpura	8 (4)
Multifocal motor neuropathy	3 (1.5)
Category B	41 (20.4)
Guillain-Barre syndrome	21 (10.4)
Myasthenia gravis (acute exacerbation)	11 (5.5)
Polymyositis (refractory)	5 (2.5)
Relapsing-remitting multiple sclerosis	2 (1)
Dermatomyositis (refractory)	1 (0.5)
Hematopoietic cell transplantation with hypogammaglobulinemia	1 (0.5)
Category C	54 (26.9)
In vitro fertilization	20 (10)
Postrenal transplantation	6 (3)
Encephalopathy	5 (2.5)
Toxic epidermal necrolysis	3 (1.5)
Adult sepsis	3 (1.5)
Systemic lupus erythematosus	3 (1.5)
Arthritis rheumatoid	2 (1)
Transverse myelitis	2 (1)
Neonatal sepsis	2 (1)
Cerebral vasculitis	2 (1)
Septic arthritis	1 (0.5)
Aplastic anemia	1 (0.5)
Wagner's disease	1 (0.5)
Hepatitis B	1 (0.5)
Autoimmune hemolytic anemia	1 (0.5)
Thrombocytopenia	1 (0.5)

Moreover, the specialty of neurology was another factor, which significantly predicted the appropriate use of IVIG in our study ($P < 0.001$). However, when the multivariate model was developed, only the factors of female gender, older age, and longer time to start IVIG administration from hospital admission remained statistically significant ($P < 0.001$, 0.024, and 0.007, respectively) [Table 3].

In our studied patients, hydration and pre-medications before using IVIG were not adequately applied for more than half of the patients (60.7% and 50.7%, respectively). However, 96% of the patients received IVIG with the safe administration rate.

Overall, 142 (70.6%) patients did not show any adverse reactions, whereas systemic (fever, headache, nausea, vomiting, and back pain) and allergic reactions occurred in 28.9% and 0.5% of patients, respectively. The rate of IVIG infusion and re-medication significantly influenced the prevalence of systemic adverse reactions [Table 4].

Table 3: Relationship between independent variables of the studied patients and the misuse of intravenous immunoglobulin

Variables	Appropriate use	Inappropriate use	OR (95% CI)		*P**
			COR	AOR	
Sex (%)					<0.001
Male	63.7	36.4	0.215 (0.133-0.349)	0.188 (0.093-0.380)	
Female	36.3	63.6	1	1	
Age (%) (years)					0.024
0-18	26	7.4	0.105 (0.038-0.295)	0.258 (0.080-0.837)	
>18	74	92.6	1	1	
Hospitalization ward (%)					
Day clinic	62.9	48.1	0.289 (0.187-0.447)	0.713 (0.420-1.211)	0.427
ICU	13.3	22.2	0.632 (0.307-1.301)	0.567 (0.209-1.536)	0.211
Surgery	1.4	1.9	0.500 (0.045-5.514)	1.292 (0.080-20.845)	0.265
Medical	22.4	27.8	1	1	0.857
Time spent from hospitalization to start IVIG (mean±SE)	4.89±0.57	15.29±2.12	0.988 (0.964-1.012)	1.052 (1.014-1.092)	0.007

*Multiple logistic regression analysis. COR=Crude odds ratio, AOR=Adjusted odds ratio, ICU=Intensive care unit, IVIG=Intravenous immunoglobulin, SE=Standard error, CI=Confidence interval, OR=Odds ratio

Table 4: Factors affecting on the occurrence of systemic reaction during the infusion of intravenous immunoglobulin

Effective factors	Patients (%)		*P*
	Systemic reaction	No systemic reaction	
Brand of IVIG			0.4*
Intratect	50 (86.2)	111 (78.2)	
Privigen	2 (3.4)	10 (7)	
IV-globulin SN	6 (10.3)	21 (14.8)	
Infusion rate			0.03*
Less than or equal to the recommended rate	53 (91.4)	139 (97.9)	
More than the recommended rate	5 (8.6)	3 (2.1)	
Premedication			0.007**
Adequate premedication or more than the recommended dose	11 (19)	55 (38.7)	
Inadequate or without intake	47 (81)	87 (61.3)	
Hydration			0.5**
Adequate hydration	21 (36.2)	59 (41.5)	
Inadequate or without intake	37 (63.8)	83 (58.5)	

*Fisher-exact test, **Chi-squared test. IVIG=Intravenous immunoglobulin, IV=Intravenous

Finally, in our studied patients, 8 out of 201 patients (4%) died during the follow-up period. Two-third of the dead patients had an inappropriate indication for using IVIG, which was statistically significant according to statistical analysis (P = 0.007). However, the duration of hospitalization was not significantly different between the groups (P = 0.476).

The brands of IVIG used in the study were Intratect® (Biotest Pharma GmbH, Germany), Privigen® (CSL Behring AG, Switzerland) and I. V.-Globulin SN (Green Cross Corporation, Korea) with the same average cost per gram of 46 US $ (in 2016). The total cost of inappropriate used IVIG in each patient was calculated by multiplying the sum of the inappropriate gram of used IVIG with the cost of each gram of IVIG.

Our results showed most of the cost of IVIG (75.4%) was dispensed for appropriate indications, while the corresponded cost of inappropriate usage was also considerable, amounting to nearly 180000 US dollar for 54 patients.

Discussion

Understanding the factors affecting the misuse of medications will enable the health providers in the implanting program to prevent inappropriate use of them, and medication use evaluation (MUE) is the cornerstone in this manner.[21] Limited worldwide availability of IVIG, increasing the demands for unlicensed use, and escalating costs, in addition to possible adverse reactions and inadequate information for IVIG use, especially in the Middle East, has been remained the evaluation of IVIG misuse as one of the priorities of MUE for several years.[9,15,17] Therefore, this study was designed to describe the use of IVIG in one of the largest academic tertiary referral hospitals in a developing country in the

Middle East. In particular, the possible factors, which might associate with the misuse of IVIG were reported properly. Furthermore, prospective description of different characteristics of IVIG use such as the dose, type of pre-medication, hydration, the rate of infusion, adverse drug reactions, and the outcomes can distinguish this study from previously conducted studies.

In this cross-sectional study, 72% of prescribed IVIG was appropriately indicated for approved indications or the off-labeled with support indications according to the FDA. Prevalence of IVIG rational prescribing was reported extensively from 36% to overwhelmingly appropriate, as >90% in previous studies.[6,9,10,14,15,17,22,23] However, high cost for the inappropriate indications is a common dilemma in different conducted studies, which is comparable with our results, indicating >3000 US dollars spent for each patient for the inappropriate indication of IVIG. The most important reason explaining the variation of rational prescribing rate is the guidelines used for the IVIG use evaluation. More than 150 unlabeled uses of IVIG were identified with a different interpretation of reviewing organizations.[4] Furthermore, the setting of evaluation (country, academic/tertiary care centers, forwards, in which studies were conducted) and the type of the study (retrospective or prospective) are different between the conducted studies. For instance, in a retrospective study, Foster *et al*., reported that >90% of IVIG uses were appropriately indicated (approved indication or support in the medical literature) in the ICUs, according to the classification developed in a Canadian Blood Services Consensus Conference.[22] Another study in a Pediatric Intensive Care Unit of tertiary referral pediatric hospital indicated that 62% of patients received IVIG for indications with the level Ia/Ib evidence, and the other cases received IVIG for indications with level II and III pieces of evidence.[9] Moreover, this high rate of compliance with the guideline was also represented in the noncritical care setting with a strict system for the IVIG prescription approval, especially in the developed countries.[5,23-25] However, the lower ranges of appropriate use of IVIG (35%–60%) were reported in other studies.[6,15,17] It should also be noted that a few studies conducted in the Middle East region also showed an inappropriate use of IVIG.[10,26-28] Anyway, some of these studies had a small sample size.[28,29]

Regarding the indications for the IVIG prescription, almost all the patients with PID receive IVIG in the day-clinic of this center. Therefore, PID serves as the most frequent indication for the IVIG administration. Furthermore, since PID is the FDA-label indication, the administration of IVIG in the day-clinic was more appropriate than the other wards. On the other hand, neurological disorders including chronic inflammatory CIDP and Guillain-Barre syndrome were responsible for near one-third of IVIG indications, which is aligned with most frequent prescriptions of IVIG by the neurologists, which is consistent with that on the literature.[18,23,24,30]

A significant higher dose of IVIG prescribed in ICU patients confirms the fact that the anti-inflammatory and immunomodulatory effects of IVIG, mainly required in the treatment of ICU patients represented in higher doses than the amount used for the immunodeficiency purposes.[1]

Despite the existence of some data regarding the IVIG use evaluation in the literature review, there was not enough information regarding the variables related to the misuse of that. We found that older age, longer time spent from admission to start IVIG and the female gender to have a significant association with the misuse of IVIG. IVIG may be considered as the last therapeutic option for the patients' survival, and attending physicians prescribe it even when there is not sufficient evidence to support the required use of the substance, which could explain that the longer time required to start IVIG from admission in these inappropriate indications. However, we could not find clear reasons to explain how demographic characteristics could affect the misuse of IVIG.

The most frequent adverse reactions in our study were the systemic reaction (about 30%), which is compatible with the declared prevalence of 20%–50% in the previous studies.[31] Moreover, another study conducted in a teaching hospital in Yazd/central Iran revealed that 26.7% of the study population developed adverse reactions (mainly mild reactions) to the IVIG in that study.[27] Our results showed that the infusion rate and pre-medication significantly affected the occurrence of adverse reactions, which is compatible with the medical literature.[32] However, the brand of IVIG and hydration did not have any significant effects on these reactions. The recent review of adverse reactions of IVIG declared that the most reported adverse reactions of IVIG are associated to the infusion rate. Furthermore, appropriate hydration may also reduce the incidence of delayed or late events such as a migraine headache, aseptic meningitides, deep vein thrombosis (DVT), and renal impairment, and its role to decrease the systemic reactions is imprecise.[33]

Although adverse effects, known to be associated with IVIG, were reported in our study, they were limited by some confounders. For instance, the systemic reactions such as fever, nausea, and vomiting or back pain might be attributed to many conditions, in which IVIG was

prescribed. On the other hand, some adverse reactions such as DVT or renal insufficiency were delayed and could not be detected in a limited time of our study. Moreover, they could be contributed to other conditions with similar adverse reactions.[31]

The low hospital mortality presented in our study is compatible with some previous studies.[15] However, it is much lower than mortality rate (55%) reported among ICU patients.[22] The high rate of mortality could be related to the critical condition of these patients, whereas in our study, >60% of patients received IVIG in the day-clinic. Besides, our results showed that the mortality was also significantly higher among patients with inappropriate indications.

Even though this study opened a new window to look into the various aspects of IVIG use, it should be mentioned that these data may be limited by some factors. First, this study was conducted in a regional hospital over a short period. Second, our population may not be suitable represent for all groups of patients, especially in the pediatric practice. On the other hand, the results in the referral university hospital with rare diseases and refractory patients to conventional therapy may be different to that from other hospitals.

However, different policies have been implemented in clinical settings to control the IVIG prescription, but at the time of our study, the IVIG was dispensed according to the physician orders without any control on its use in our center. Thus, it was necessary to use an approved guideline to control the substance use in different wards of the hospital and provide the opportunity for effective feedback to develop and revise this guideline. Therefore, after completing this study, a clinical guideline was introduced in this tertiary, academic center by the drug hospital committee in collaboration with the expert specialists. Afterward, the month-by-month analysis of the IVIG use could be performed to assess the possible changes in the IVIG use after implementation of the guideline. However, the expert opinion for the use of IVIG in the off-label (without sufficient evidence), but life-threatening condition would limit this practice which was also mentioned in previous studies.[10]

Because of the different interpretation of clinical evidence by the specialists, the acceptability of unlabeled indications of IVIG is inconsistent in various guidelines of healthcare institutions. However, the institutional guideline is necessary for the delineation that patients benefit from the IVIG use and limit prescription of IVIG for the unlabeled indications by the implementation of some control mechanisms.[4]

In this prospective study, >70% of patients received IVIG with appropriate indications defined by the FDA indications, in the academic tertiary care setting. Implementation of clinical practice guideline is necessary to limit the IVIG use for the inappropriate indications. Furthermore, more attention to patients, who are at risk for the inappropriate use of IVIG will have a significant impact on the rational use of IVIG. Moreover, the required compliance with premedication and suitable rate of IVIG infusion could limit the immediate common adverse events.

Authors' Contributions

Shadi Farsaei and Ali Mohammad Sabzghabaee provided the concept and the idea of the research, Zeinab Fakhari gathered the data, Shadi Farsaei and Ali Mohammad Sabzghabaee analyzed the data and prepared the drafted manuscript. All authors contributed in revising the final version and approved it for submission.

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Conflicts of interest

There are no conflicts of interest.

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