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Original Article

Intravenous Immunoglobulin Utilization in a Pediatric Tertiary Care Teaching Hospital in Iran

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Abstract

Intravenous immunoglobulin (IVIG) is an expensive medicine which is widely used for unlabeled indications. We conducted this drug utilization review (DUR) to evaluate the appropriateness of IVIG utilization in Tehran, Iran. This cross sectional study was conducted in a referral pediatric tertiary care hospital in Tehran. During a three month period in 2015, medical records of inpatients with IVIG order were evaluated. Appropriate indications for IVIG were determined based on the evidenced based guidelines and literature. Medical records of patients were reviewed and demographic data as well as the diagnosis, previous treatments, IVIG indication, dose, duration and the adverse drug reactions (ADR) were documented. Additionally, cost of therapy was calculated. During the study, 115 patients received IVIG. In 51 cases (44.4%), a total of 1338 gram IVIG was administered inappropriately. We found that in 32 cases (27.8%), intractable epilepsy was the inappropriate indication. The most frequent prescribers of IVIG were clinical specialists of pediatric neurology, pediatric asthma and immunology followed by pediatric hematology. In terms of safety, we found that 64 (55.6%) patients experienced at least one ADR. The most prevalent ADRs were hypotension (27.8%), fever (26.9%) and chills (18.3%). Total cost of IVIG during the study period was 6,075,500,000 Rials (approximately 215,872 $). Irrational use of IVIG is still a considerable issue that costs a considerable amount. Due to the high cost of therapy, multifaceted interventions are necessary to be implemented to improve the prescribing practice.

Keywords: Adverse Drug Reactions, Drug Utilization Evaluations, Drug Utilization Review (DUR), Intractable Epilepsy, Intravenous Immunoglobulin (IVIG), Rational Use

1. Introduction

Intravenous immunoglobulins (IVIGs) are therapeutic plasma protein derivative preparations [1, 2] which are manufactured from the IgG of healthy individuals [1]. In the late 1970s, IVIG was first developed for the

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treatment of congenital hypogammaglobulinema [3]. However, the understanding of the anti-inflammatory and immunomodulatory properties of IVIG, led to the utilization of this agent in autoimmune and systemic inflammatory conditions [4]. Treatment of immune thrombocytopenic purpura (ITP) was the first indication in which the immunomodulatory actions of IVIG was recognized [3]. Moreover, in Kawasaki disease, immune-mediated neurologic disorders such as Guillain-Barre syndrome, chronic idiopathic demyelinating polyneuropathy (CIDP), multifocal neuropathy with conduction block and acute myasthenia gravis this medication was used successfully [1]. However, the therapeutic applications of IVIG were not limited to the mentioned indications and were expanded for the treatment of a variety of other conditions [5-7]. In fact, the clinical use of IVIG expanded as much as it was once suggested that "it would be difficult to find an autoimmune or an inflammatory condition for which IVIG has not been attempted" [3]. Despite the wide range of clinical utilization, the FDA-approved indications for IVIG are limited to primary humoral immunodeficiency, multifocal motor neuropathy, B-cell chronic lymphocytic leukemia, ITP, Kawasaki disease and CIDP [8].

WHO defines drug utilization review (DUR) as "a system of ongoing, systematic, criteria-based evaluation of drug use that will help ensure that medicines are used appropriately" [9]. Conducting DUR was proposed to be one of the main modules applied for cost control and quality assessment [10]. IVIG has special features that make it permissible to be a target in DUR and medication use evaluation studies. First of all, it was reported that more than half of the IVIG administrations were not licensed [4]. Considering the wide indication for utilizations of IVIG, it seems that it is necessary to evaluate wheatear the utilizations are appropriate or not. Moreover, another feature is the high cost of therapy with IVIG [11]. Since, this medicine is very expensive, the cost of a course of therapy is considerably high even despite the insurance coverage. This high cost of therapy with IVIG is not only limited to Iran, but is similar in other countries [2]. Finally, unfortunately unlike many other countries, no national drug protocol has been developed for IVIG administration in Iran to limit the irrational use of this medication.

Generally, DUR is aimed to direct the drug therapy to become appropriate and more cost effective [10]. Additioanlly, it can provide data for implementing DUR programs which consists of planning and enforcement of interventions and ultimately assessment of the results of the interventions toward rational use of drugs [12]. To the best of our knowledge,

there are limited studies that have evaluated the utilization of IVIG in hospital settings in Iran [13, 11] as well as other countries [14-15] preveiously. So, the current study was designed to evaluate the appropriateness of IVIG administration and treatment cost in a pediatric hospital compared to the previous evaluation in the same setting.

2. Materials and Methods

2.1. Study Setting

This cross sectional study was conducted in Children's Medical Center, a pediatric tertiary care teaching hospital affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study was performed prospectively over a 3-month period from March to June 2015.The study hospital is one of the main referral children hospitals in Iran.

2.2. Data collection

During the study period all of the inpatients with IVIG order were identified through the hospital information system (HIS). Then, the charts of the patients were reviewed in wards and the required data were documented. The recorded data included patients' demographics, diagnosis, previous treatments, IVIG indication, dose and duration of treatment. Additionally, the ADR experienced by patients were recorded based on the documentation in the patients' charts and according to the online Lexicomp IVIG drug information monograph. Whenever the required data were not included in the patients' medical records the researcher contacted the physicians and/or nurses.

2.3. Assessment of Appropriateness

In order to determine the rational use of IVIG, the indications were categorized into 5 groups using the framework proposed by Alangari *et al.* [14] and based on the recommendations from consensus guidelines. The categorization of the indications were as follows: A) Administration based on FDA-labeled indication, B) off-labeled indication recommended as first line; C) off-labeled indication recommended as an alternative; D) not recommended and N) lack of evidence for administration (Table 1).

Based on this categorization, IVIG administration was considered appropriate if the drug was prescribed for indications in A or B category. For indications in the C category only if the IVIG was administered as a second-line agent, the treatment was considered appropriate. Moreover, all of the IVIG administrations in D or N categories were assumed to be inappropriate.

2.4. Drug Costs

The total dose of IVIG administered for each patient was recorded during the study period. The cost per gram IVIG was calculated based on the average price of the available preparations in the hospital which was 1450000 Rials (approximately $ 51.5 at the study time). IVIG was always ordered by generic name and none of the prescribers insisted on a special preparation.

2.5. Statistical Analysis

Descriptive characteristics were reported by frequency (percent) for qualitative variables

Table 1. Distribution of indications for IVIG administration within each category, and the number of patients and compliance with guideline suggested dosing regimen

Category	Indication	Recommendations	Patients N (%)	Compliance with Dosing Regimen N (%)	Total IVIG (g) (%)
A FDA-Labeled	ITP	First-line treatment: A single dose of IVIG (0.8-1g/kg) or a short course of corticosteroids. More rapid increase in the platelet count is achieved with IVIG [16]	16(14)	10 (62.5)	683 (16.3)
	Kawasaki Disease	Single infusion of IVIG, 2 g/kg together with aspirin. If possible this treatment should be initiated within 7 days of illness or within the first 10 days of illness [17]	17 (14.7)	10 (58.8)	991 (23.6)
	Primary Immunodeficiency	IVIG is recommended with starting dose of 400-600 mg/kg every 3-4 weeks [18]	13(11.3)	7 (53.8)	154 (3.6)
	Total patients with A indications		46(40)		1828 (43.6)
B Off-labeled Indication Recommended as First Line	Guillain-Barre Syndrome	Total dose of 2 g/kg, given as 1 g/kg for two days or 400 mg/kg for five days [19]	9 (7.8)	6 (66.7)	724(17.2)
C Off-labeled Indication Recommended as Alternative	Autoimmune Hemolytic Anemia	IVIG is not recommended as a routine treatment option. It may be considered one option among adjunctive therapies in urgent situations [20]. Very high doses may be required: 1 g/kg/ day for five days. Up to 2 g/kg [21]	5 (4.3)	None (0)	235(5.6)
	Neonatal thrombocytopenia	IVIG dose is 1 g/kg. If thrombocytopenia persists occasionally more than 1 dose is required [22]	4 (4.3)	3 (75)	65 (1.5)
	Total patients with C indications		9 (7.8)		300 (7.1)
D Not Recommended	Neonatal sepsis	IVIG has no effect on the outcomes of suspected or proven neonatal sepsis [23]. Routine use of IVIG for the prevention of mortality for suspected or proven neonatal infection is not recommended [24]	8 (6.9)	None (0)	76 (1.8)
N Lack of Evidence	Refractory epilepsy	No convincing evidence support the use of IVIG and its efficacy for epilepsy and no reliable conclusion [25]	32 (27.8)	15	1080(25.7)
		Other indicatons[1]	11 (9.5)	-	182 (4.3)
	Total patients		**115 (100)**		**4190(100)**

ITP: Immune Thrombocytopenic Purpura, IVIG: Intravenous immunoglobulin. [1]Other indications consisted of Stevens–Johnson syndrome (N=2), Hemophagocytic Lymphohistiocytosis (HLH) (N=2), Acute Disseminated Encephalomyelitis (ADEM) (N=1), End stage renal disease (ESRD) (N=1), Myocarditis (N=1), Polydermatomyositis (N=1) and unknown (N=3)

and mean (SD) for quantitative variables. Frequencies and proportions of indications in each category were reported. Comparing incidence of ADR between groups was performed using chi square test.

3. Results and Discussion

A total of 115 patients including 62 (53%) boys who received IVIG in the hospital were evaluated in this study. Mean age of patients was 4 years and ranged from neonates to 16 year-old children. The most frequent prescribers of IVIG were clinical specialists of pediatric neurology, pediatric asthma and immunology and pediatric hematology. Number of patients within each indication category and the compliance with the dosing regimens based on guidelines are shown in Table 1.

Only in sixty four cases (55.6%), the IVIG administrations were considered to be appropriate (categories A, B, or C). The irrational prescribing was responsible for about one third of the total amount of dispensed gram IVIG (Table 2). The total amount of IVIG consumed during the first DUR was 4190 grams. The average dose administered per patient with the indications in the A and B category was 1 g/kg and 0.51 g/kg respectively. Additionally, the average dose per patient was 0.81 g/kg, 0.5 g/kg and 0.82 g/kg for patients with the indications in the C, N and D categories respectively.

3.1. Patients' Safety and ADRs

We found that 64 (55.6%) patients experienced at least one ADR. The most prevalent ADRs were as follows: hypotension (N=32, 27.8%), fever (N= 31, 26.9%), chills (N=21, 18.3%), vomiting (N=12, 10.4%), nausea (N=11, 9.6%), shortness of breath (N=10, 8.7%), headache (N=10, 8.7%), respiratory wheezing (N=7, 6.1%) and hypertension (N=5, 4.3%). Less than 5% of patients experienced palpitations and chest pain. The frequency of ADRs in different patients' age groups is shown in table 3. We found that there was a significant association between the frequency of ADRs and age groups (*P*-value: 0.008, Chi square: 11.7). The

Table 2. Amount of the appropriateness and total IVIG administered to patients for each category.

Indication	Categories	Patients N (%)	Grams IVIG (%)
Appropriate Indications	A , B ,C	64 (55.6)	2852(68.1)
Inappropriate Indications	N,E and others	51 (44.2)	1338 (31.9)

Table 3. Frequency of ADRs in each age group.

ADR / Age	<1 year old N (%)	1-3 years old N (%)	3-6 years old N (%)	>6 years old (%) N	Total
With at least one ADR	11 (36.6%)	23 (63.8%)	13(86.6%)	17 (50.0%)	64 (55.6%)
Without ADR	19 (63.3%)	13 (36.1%)	2(13.3%)	17 (50.0%)	51 (44.4%)
Total patients	30	36	15	34	115

range of ADR in age groups varied between 36.6% in less than one year-old patients to 86.6% in patients with 3 to 6 years- old.

No significant correlation was noted between the incidence of ADR and sex (*P*-value: 0.84, Chi squared =0.042). The prevalence of ADR in patients with different indication for IVIG was significantly different (*P*-value: 0.001). High frequency of ADRs were noted in patients with Kawasaki disease (N=15, 88.2%), ITP (N=13, 81.2%), Guillain-Barre (N=6, 66.7%), immunodeficiency (N=8, 61.5%) and intractable epilepsy (N=14, 43.7%).

3.2. Cost of Treatment

The mean cost of IVIG for each category of indications is listed in table 4. As shown in the table, total cost of IVIG during a 3-month period was 6,075,500,000 Rials (approximately 215,872 $).

3.3. Discussion

This study was primarily conducted to evaluate the clinical use of IVIG in a pediatric tertiary care teaching hospital in Iran. In particular, we aimed to assess the rational use of IVIG according to the evidenced based pediatric guidelines. We found that 44.2% of patients received IVIG inappropriately which was accounted for administration of 1338 (31.9%) gram IVIG in a three month period. This inappropriate utilization incurred a considerable cost of 1,940,100,000 Rials to the patients and health care systems.

The current study was conducted in the same medical center as the study by Dashti-Khavidaki *et al*. which was performed in 2008 [11][11]. The comparison of the results showed that the number of patients who received IVIG dramatically increased from 46 patients during a 6-month period to 115 patients during a 3-month period in the current study. Similar increase in IVIG utilization was also reported in a survey by Sarti *et al.* They revealed that the administration of IVIG increased during a four-year period from 2003 to 2006 in Italy despite concerns regarding the long-term safety and future availability [26]. A similar trend was also reported by Wu *et al*. in a study in two pediatric hospitals between 2000 and 2009 in Singapore [27]. Moreover, globally, a threefold increase in the annual consumption of IVIG was noted during a 15-year period [28]. In the previous study in the current study center, 39.6% of IVIG administrations were due to ITP, 22.9% for the treatment of Guillain-Barre syndrome, 18.7% for patients with Kawasaki disease, 16.7% for intractable seizure and 2.1% for neonatal hemolytic anemia [11]. However, in the current study the percentages of patients who received IVIG for ITP, Guillain-Barre syndrome and Kawasaki disease decreased. But the percentages of patients who received IVIG for intractable seizure and neonatal hemolytic anemia increased. Additionally, as presented in table 1, patients with several other indications received IVIG at this time.

It should be noted that in this center there was not a systematic policy for the restriction of IVIG administration for unlabeled or inappropriate clinical conditions. One of the unapproved indications for IVIG is intractable

Table 4. Mean dose and cost of IVIG for each category of indications.

Indications		*Category*	*Gram IVIG*	*% of Total IVIG Administration*	*Estimated Cost (Rials)*
Labeled Indication		A	1828	43.6	2,650,600,000
Unlabeled Indications	Recommended as First Line	B	724	17.3	1,049,800,000
	Recommended as Alternative	C	300	7.2	435,000,000
	Not Recommended	N	76	1.8	110,200,000
	Lack of Evidence	E	1080	25.8	1,566,000,000
	Other Indications	-	182	4.3	263,900,000
Total			4190	100	6,075,500,000

childhood epilepsy. IVIG is not recommended for this indication in the evidence-based guidelines for hematologic and neurologic conditions published in 2007 [29] Moreover, in France in 2010, IVIG for refractory epilepsy was among the clinical conditions under evaluation by the comité d'évaluation et de diffusion des innovations technologiques [1]. Additionally, in Australia, based on 2012 criteria, the use of IVIG for epilepsy was limited only to Landau–Kleffner and Lennox–Gastaut syndrome when “all conventional therapies” have failed and “full assessment” was performed by a pediatric neurologist [30]. In contrast, Mikati *et al*. found that 43% of 37 patients with intractable childhood epilepsy experienced more than 50% decrease in seizures with IVIG which was a significant reduction [31]. However, it should be noted that the mentioned study was open-labeled, uncontrolled and the only study which reported a significant reduction in seizure with IVIG. Based on the weakness of evidences in this regard and lack of current guidelines support, the administration of IVIG for this indication in the present study was considered irrational. Moreover, the frequency of IVIG administration for this indication was very high compared to other studies which can be granted as an evidence for irrational use in our center. For example, in a retrospective study in Saudi Arabia, Alangari *et al.* evaluated 305 patients (including 170 children) who received IVIG in a 3 year period. They reported that only 6 children (2%) received IVIG for intractable childhood epilepsy [14]. Moreover, in a ten-year study of IVIG use in 1009 patients in two major pediatric hospitals in Singapore, intractable epilepsy was among the clinical conditions for which less than 5% of patients received IVIG [27]. Similarly, in a study in Canada in which IVIG administrations in 2 pediatric teaching hospitals were evaluated between 1997 and 1998, epilepsy was among the indications for which less than 5% of total annual IVIG was used [32].

We found that the most frequent ADR experienced by our patients was hypotension. Additionally, children with various IVIG

indications were significantly different in terms of experiencing ADRs. Totally 64 cases (58%) experienced at least one ADR, which was higher than the previous studies. For example, Wu *et al.* noted that 6.5% of pediatrics experienced ADR with IVIG and the incidence was not significantly higher in patients with any special diagnosis [27]. In another study on 554 patients receiving IVIG including 87 (15.7%) children and adolescents in 13 tertiary hospitals in Spain, only 21.4% of patients experienced at least one ADR and 5% experienced serious ADRs [2]. However, the number of pediatric patients with ADR was not separately reported. Prasad *et al.* also mentioned that in 3-15% of patients, systemic ADRs to IVIG was observed, which were usually self-limiting and could be avoided by decreasing the infusion rate [33]. So, the higher frequency of ADRs in the current study, worth to be evaluated in further studies.

3.4. Limitations

In the current study, the documentation of ADRs was based on the nursing notes in patients' medical records. This method of detecting ADRs might have weakness regarding the assessment of causality and the severity of ADRs.

4. Conclusion

Irrational use of IVIG is still a considerable issue not only due to the safety concerns and ADRs but also due to the high costs of therapy. We found that the educational interventions and necessity for completion of an order form by prescribers for a single indication in neurology ward did not result in considerable decrease in the irrational use of IVIG in patients with intractable epilepsy. National protocols as well as the other interventions are needed to be implemented simultaneously to reduce the inappropriate prescriptions.

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