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Original Article

Pharmacology Section

Analysis of Off-label use of Intravenous Immunoglobulin in a Tertiary Health Care Facility: A Record-based Cross-sectional Study

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ABSTRACT

Introduction: The off-label clinical use of Intravenous Immunoglobulin (IVIG) has increased despite the existence of its approved indications by drug regulatory agencies. IVIG is an expensive drug and its availability is also limited; hence, judicious use of IVIG is highly recommended.

Aim: To evaluate the utilisation pattern and cost burden of IVIG in the In-Patient Departments (IPD) of a tertiary healthcare facility.

Materials and Methods: This record-based cross-section observational study was carried out in the IPD of MKCG Medical College, Department of Pharmacology, MKCG, MCH, Berhampur, Odisha, India, from September 2022 to September 2023, where a total of 108 patients who were prescribed and received IVIG for any clinical condition were included. Clinical data, like clinico-demographic profile, diagnosis, dosage and duration of IVIG, were collected in a predesigned structured Case Record Form (CRF). The utilisation pattern was compared with the drug regulatory agencies' United States Food and Drug Administration (USFDA) approved IVIG conditions to determine the proportion of such use. Data were collected, compiled and analysed using MICROSOFT (MS) Excel and Statistical Package for Social Sciences (SPSS) version 25.0. Data were expressed as frequency, percentages, median and interquartile range.

Results: The median age of patients who received IVIG was 12 years and Interquartile Range (IQR) was 29 (Q1=3, Q3=32). Majority of the cases receiving IVIG, i.e., 59 (54.6%), were from paediatrics IPD. The proportion of male patients was higher at 57 (52.7%). Guillain-Barré Syndrome (GBS) was the most common off-label indication, accounting for 55 (50.9%), followed by Multisystem Inflammatory Syndrome (MIS-C) in 12 (11.1%) children. In 73 (67.59%) of cases, IVIG was administered for off-label indication, 8 (6.48%) of cases for FDA-approved indication and remaining for others. The highest expenditure was done on diseases with off-label indications, which accounted for 88.63% of total expenditure for IVIG.

Conclusion: In the present study, the use of IVIG for off-label indications was higher than for approved indications. National or local drug protocols are needed to prescribe more rational IVIG utilisation and assist physicians to use IVIG for approved or high evidence-based indications.

Keywords: Cost-analysis, Drug regulatory agencies, Drug utilisation

INTRODUCTION

The IVIG is widely utilised as a replacement therapy for immunodeficiency conditions, as well as a treatment for various autoimmune and inflammatory disorders [1]. IVIG is a sterile biological product composed of concentrated antibodies extracted from the plasma of at least one thousand individual donors, adhering to the minimum standards set by the World Health Organisation (WHO) [2]. This diverse donor pool contributes to IVIG's broad-spectrum efficacy, encompassing numerous specific antibodies effective against various infectious and autoimmune diseases [3]. Typically, the preparation comprised of more than 95% IgG, minimal IgA and traces of other immunoglobulins [4]. Initially employed in 1981 to treat Immune Thrombocytopenia (ITP), IVIG has since become a standard treatment for a wide spectrum of diseases, including haematologic, neurologic, rheumatologic, dermatologic and nephrological conditions [5]. The US Food and Drug Administration (USFDA) [6] and the European Medicines Agency (EMA) [7] have approved IVIG for several indications, such as primary immunodeficiency, ITP, Kawasaki disease, bone marrow transplantation, B-cell chronic lymphocytic leukaemia, paediatric HIV, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and multifocal motor neuropathy [8].

Additionally, IVIG is prescribed off-label for numerous conditions, such as autoimmune and ocular diseases, neurologic disorders, GBS, haemolytic disease of the newborn and Myasthenia Gravis (MG) [8-10]. Despite its proven efficacy for specific conditions, the use of IVIG has expanded too many off-label indications, often without adequate clinical evidence. This irrational prescribing trend, coupled with the high cost and limited availability of IVIG, underscores the importance of studying its utilisation pattern [11].

In the Indian context, IVIG is most commonly used in dermatomyositis, lupus erythematosus, autoimmune blistering diseases, vasculitis, Toxic Epidermal Necrolysis (TEN) and Scleromyxedema [12]. IVIG can cause several adverse drug reactions, ranging from mild to severe, typically occurring within the first hour of infusion. Drug Use Evaluation (DUE) studies review medication use against predetermined standards and are essential for ensuring appropriate IVIG utilisation.

Although IVIG has a limited number of FDA-approved indications, its off-label use is escalating day by day. A study reported that 52% of study subjects from twelve different institutions received IVIG for off-label indications, with no positive clinical outcome observed in 20% of the off-label group and 12% of the labelled group [13]. Despite limited evidence supporting off-label indications, over 150 such uses have been reported among prescribers, incurring substantial cost burden to the healthcare system [14]. In Iran, IVIG was categorised as one of the top consumed drugs in the year 2017 as well as 2020, prompted the Ministry of Health and Medical Education of Iran to advocate for its rational use [15].

In the present healthcare facility, there is also a lack of studies on IVIG prescribing patterns and costs across different patient and prescriber

groups, highlighting the need for further research. Therefore, the present study aimed to investigate the off-label utilisation pattern of IVIG in terms of its indications, evidence level, dosage and strength based on USFDA guidelines, as well as the cost burden in a tertiary care teaching hospital of Southern Odisha.

MATERIALS AND METHODS

This record-based cross-sectional observational study was carried out in the IPD of various departments in collaboration with Department of Pharmacology, MKCG, MCH, Berhampur, Odisha, India, from September 2023 to October 2023. All the admitted inpatients of any departments who had ever received IVIG for any clinical condition from September 2022 to September 2023 were included. Ethics committee approval was taken before the start of the study from the Institutional Ethics Committee, MKCG Medical College, Berhampur (Memo no: 1281/Chairman-IEC, MKCG Medical College, Brahmapur-4, dated 13/09/2023). A total of 108 patients were included who met all the inclusion and exclusion criteria.

Inclusion criteria: Data from all the patients who were admitted to the hospital (IPD) and received IVIG for any clinical condition were included in the study.

Exclusion criteria: The records with incomplete patient details were excluded from the study.

Study Procedure

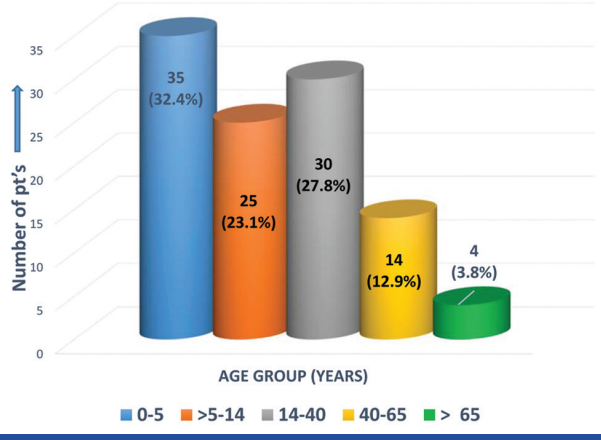
A predesigned CRF was used to gather the data such as patient's demographic details (age, gender), admission to which indoor department to which they were admitted, presenting clinical features, primary diagnosis, IVIG prescription details (dose, dosing schedule and duration) and cost. Based on US FDA guidelines, all the diagnoses were categorised into three types: labelled indication, off-labelled with strong evidence support and off-labelled with no evidence to support [6]. All the collected data were compared with the USFDA-approved indications [6].

STATISTICAL ANALYSIS

Data were entered in Microsoft Excel worksheet, double-checked and analysed. International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS), software version 25.0, was used for analysis. The data were described using frequency, percentage, mean±SD, median and IQR.

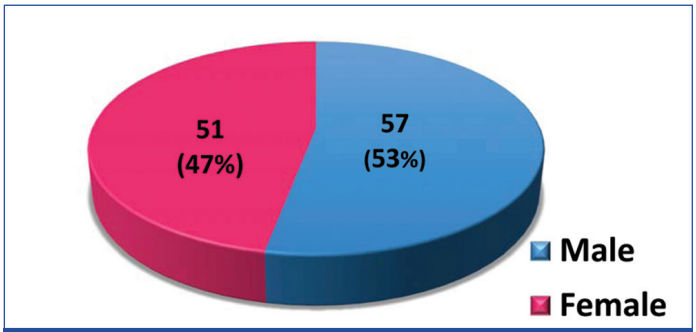
RESULTS

Out of total of 108 patients who received IVIG, the highest frequency of IVIG were prescribed to the patients who belonged to 0-5 years of age i.e., 35 patients (32.4%). This was followed by 14-40-year age group of patients i.e., 30 patients (27.8%) and 5-14-year age group, which comprised 25 patients (23.1%) [Table/Fig-1]. The median age of patients receiving IVIG was 12 years, with an interquartile range of 29 (Q1=3, Q3=32).



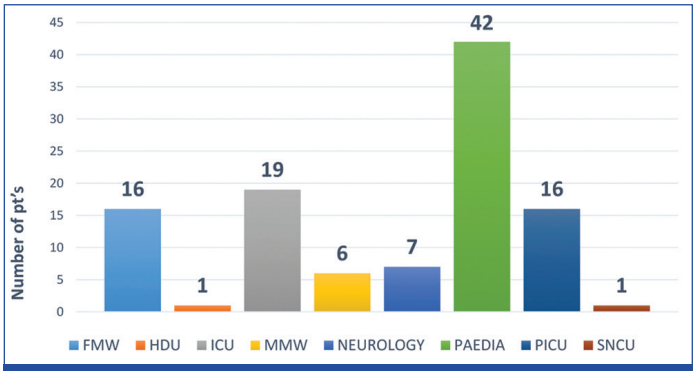
[Table/Fig-1]: Age-wise distribution of patients who received IVIG (N=108).

Considering the gender distribution of IVIG utilisation, highest amount of IVIG was prescribed to male patients which was 53% and rest 47% of total patient group who received IVIG were females [Table/Fig-2].



[Table/Fig-2]: Gender-wise distribution of IVIG utilisation pattern (N=108).

Maximum IVIG were prescribed to patients who were admitted in general paediatrics indoor i.e., 42 patients (38.9%) followed by the Mother and Baby Unit (MMU) where 19 patients (17.6%) were admitted and given IVIG and the Female Medicine Ward (FMW), where 16 patients (14.8%) received IVIG [Table/Fig-3].



[Table/Fig-3]: Department-wise distribution of IVIG utilisation (N=108).
FMW: Female medicine ward; HDU: High dependency unit; ICU: Intensive care unit; MMW: Male medicine ward; PICU: Paediatric intensive care unit; SNCU: Special newborn care unit

According to frequency of IVIG prescribed based on primary diagnosis, highest frequency of IVIG was prescribed to GBS patients (50.92%), followed by those diagnosed with pneumonia (11.11%) and sepsis (7.41%), respectively [Table/Fig-4].

Indications	Labelled indication	Off-labelled with strong evidence support	Off-labelled with no evidence to support	n (%)
AES	--	√	--	5 (4.63)
Encephalopathy	--	--	√	7 (6.48)
GBS	--	√	--	55 (50.92)
Hypokalemic palsy	--	--	√	1 (0.93)
ITP	√	--	--	6 (5.55)
KD	√	--	--	1 (0.93)
Leukaemia	√	--	--	1 (0.93)
Meningitis	--	--	√	3 (2.78)
MG	--	√	--	5 (4.63)
Pneumonia	--	--	√	12 (11.11)
PUO	--	--	√	2 (1.85)
Sepsis	--	√	--	8 (7.41)
WAS	--	--	√	2 (1.85)
Total				108 (100)

[Table/Fig-4]: Frequency of IVIG prescribed based on primary diagnosis (N=108).
AES: Acute encephalitis syndrome; GBS: Guillain Barré syndrome; ITP: Immune thrombocytopenic purpura; KD: Kawasaki disease; MG: Myasthenia gravis; PUO: Pyrexia of unknown origin; WAS: Wiskott-Aldrich syndrome

Out of total number of patients diagnosed with diseases that belong to US FDA labelled indication category, the highest amount of IVIG

was prescribed to patients with Immune Thrombocytopenic Purpura (ITP), patients that is 5.55%, followed by Kawasaki disease and leukaemia. For US FDA off-labelled with strong evidence support, maximum patients who were given IVIG were diagnosed with GBS which was 50.92%, followed by sepsis and MG and for FDA, off-labelled with no evidence to support category, 11.11% of patients received maximum IVIG who were diagnosed with pneumonia [Table/Fig-5].

Uses / Rank	Labelled indication	Off-labelled with strong evidence support	Off-labelled with no evidence to support
1st	ITP (5.55%)	GBS (50.92%)	Pneumonia (11.11%)
2nd	Kawasaki disease	Sepsis	Encephalopathy
3rd	Leukaemia	Myasthenia Gravis (MG)	Meningitis

[Table/Fig-5]: Frequency of utilisation of IVIG based on USFDA indications.

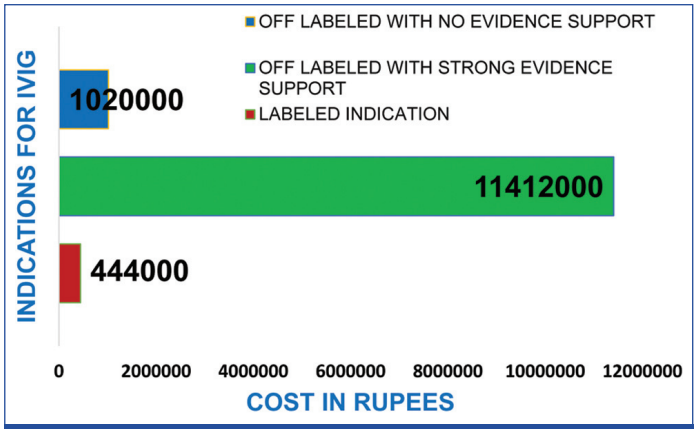
Total amount of IVIG used during the present study was 1,113 bottles. Each bottle contains 100 mL of 5% human normal immunoglobulin, which is equivalent to 5 gm in 100 mL solution. Therefore, in total of 5,565 gm of IVIG was used during the study period. A total of 108 patients were included in the study, indicating that each patient, irrespective of age, received an average of 10.30 bottles of drug, which is equal to 51.5 gm. The mean duration for which a patient received IVIG, irrespective of age and indication, was found to be 2.50 days.

Among labelled indications, patients of ITP received 26 bottles of IVIG which is 130 gm in total. Similarly, patients with Kawasaki disease received five bottles (25 gm) and those diagnosed with leukaemia received only six bottles of IVIG which is equal to 30 gm. Amongst off-labelled indications with strong evidence support, patients who were diagnosed with GBS received 849 bottles of IVIG in total (4,245 gm), while for off-labelled indication with no evidence to support, patients diagnosed with pneumonia received 27 bottles (135 gm) of IVIG in total [Table/Fig-6].

Indications	Diseases	Total dose (gram)	Average dose (gram)	Average duration of receiving IVIG (days)
Labelled indication	ITP	130	21.67	1.33
	Kawasaki disease	25	25	1
	Leukaemia	30	30	1
Off-labelled with strong evidence support	GBS	4,245	77.18	3.41
	Sepsis	170	21.25	1.5
	Myasthenia Gravis (MG)	445	89	4
Off-labelled with no evidence to support	Pneumonia	135	11.25	1.41
	Encephalopathy	130	18.57	1.57
	Meningitis	30	10	1

[Table/Fig-6]: Dose, duration of IVIG use based on US FDA indications.
*All the patients irrespective of age, gender, in patient admission department and diagnosis received IVIG as once daily dosing for above-described duration

A total expenditure was Indian Rupee (INR) 1,14,12,000 for diseases with off-labelled with strong evidence support whereas, INR 10,20,000 was spent on diseases with off-labelled with no evidence support. From the above data it is concluded that the highest expenditure was done on diseases with off-labelled use with strong evidence support, which was 88.63% of total expenditure for IVIG [Table/Fig-7].



[Table/Fig-7]: Total cost of IVIG use on different indication.

DISCUSSION

In the present study, the utilisation pattern of IVIG showed that maximum number of patients who received IVIG were diagnosed with diseases that fall under off-labelled with strong evidence support and the highest expenditure was done for diseases with off-labelled with strong evidence support.

The frequency of male patients who received IVIG was more as compared to females, the ratio being 53% to 47%, respectively. The study resembles a study done in a tertiary care teaching hospital in Sari, Iran, where the male-to-female ratio was 61.1% to 38.9% [15]. In contrast, a Malaysian study showed that 43% of total patients receiving IVIG were males and 57% were females [15]. In our current study, this might be due to inclusion of more male participants and higher prevalence of autoimmune diseases (Kawasaki disease and primary immunodeficiency disorders) in males. In diagnostic and treatment practices there may be gender biases in diagnosing and treating autoimmune diseases, with males being more likely to receive IVIG.

The present study showed that the highest frequency of IVIG was prescribed to patients from the paediatrics department, i.e., 38.9%. This study finding corroborate with a study done in Malaysia [16], where 33.3% of prescribed IVIG was from the paediatric department. Similarly, a study done in Sari [15] shows that 48.7% of patients prescribed IVIG were from the paediatrics department. This type of usage pattern might be due to prevalence of paediatric diseases like Kawasaki disease, ITP and GBS, which are common in children and require treatment of IVIG. Besides severe viral and bacterial infections in children often require IVIG for passive immunity and immune modulation. Other neurological conditions like autoimmune encephalitis in children, may be aggressive, necessitating treatment by IVIG. According to certain clinical guidelines and practices, established paediatric protocols frequently recommend IVIG for various conditions which are more prevalent or severe in children [17,18].

The present study depicted that 67.59% of IVIG treatment was prescribed for evidence-based off-label usage, 7.41% was for FDA-approved indications, whereas 25% were for non authorised and non approved indications. This distribution aligns with a study [16] but diverges from another [15]. For instance, a similar study conducted in Toronto reveals that over 80% of the patients received IVIG for indications supported by published recommendations, with 47.5% of the cases falling under the lower evidence category [19]. Contrary to the present study, a study at a tertiary hospital in Sari [15] reports that 62.8% of IVIG administrations were consistent with FDA-approved indications, 21.2% were for evidence-based off-label uses and 16% were for non authorised and non-accepted indications. A Spanish study reported that 60% of IVIG use was for FDA-approved indications, with 16% for evidence-supported off-label use and 24% for unsupported off-label uses [20]. Similarly, a retrospective study focusing on paediatric patients found 77.3% adherence to FDA-labelled indications [21] and Fakhari Z et al., observed that 72% of IVIG use was appropriate, including both FDA-labelled and off-label uses with solid evidence [14]. Contrary to the current study findings, a study in Canada reported that 89% of IVIG use was deemed appropriate according to guidelines [22]. This contradicted with studies from Iran, where more than half of IVIG use was for FDA-labelled indications [15,23], suggesting variability

in practice patterns across different regions [24,25]. This variability underscores the importance of localised guidelines and evaluations of rational use.

This might be due to limited treatment options; for some rare or complex diseases, IVIG may be one of the few effective treatment options available. Continuous research supports the efficacy of IVIG in treating conditions not originally indicated, thereby expanding its off-label use. In critical care settings, IVIG can provide a quick therapeutic response for severe, life-threatening conditions. Conditions with complex, multifactorial aetiologies, such as certain autoimmune and inflammatory diseases, may also be benefited from broad spectrum of action of IVIG [26].

The current study identifies the most common IVIG usage to be GBS that is 50.92%, followed by pneumonia which was 11.11%, sepsis at 7.41% and encephalopathy 6.48%. A study in Sari [15] showed Primary Immunodeficiency Diseases (PID) and CIDP as the most common indications for IVIG, each accounting for 19.5% of cases, followed by GBS and ITP, each at 15%. These findings are consistent with the literature, where PID and CIDP are commonly cited as indications for IVIG [27]. Conversely, a study in Iran [23] reported ITP as the predominant indication, reflecting regional differences in clinical practice. The most common use of IVIG for GBS may be due to its high efficacy; IVIG has been proven effective in numerous clinical trials for treating GBS, leading to significant improvement in patient outcomes. IVIG is one of the main treatments recommended in clinical guidelines for GBS, alongside plasmapheresis. It can quickly halt the progression of GBS, which is crucial for preventing severe complications such as respiratory failure.

The high cost of IVIG is a major issue [16]. The current study depicted that the highest expenditure was done on diseases with off-labelled with strong evidence support which was INR 11,412,000, which constitutes 88.63% of total expenditure for IVIG. Research from a tertiary care hospital in Malaysia [16] found that the unsubsidised cost exceeded RM 900,000 (Malaysian ringgit, currency of Malayasia), that is INR 16,200,000, with 38.5% of this amount spent on low-evidence indications, thus placing a significant financial strain on the hospital. Even if this is a government set-up and all the drugs procured and provided to the patients are free of cost, but the government has to bear the huge cost burden; hence, judicious use of IVIG is highly recommended.

Another study by Alangari AA et al., in Saudi Arabia showed that off-label or non-recommended IVIG use in two-thirds of the population resulted in costs amounting to $431,325, which is equivalent to INR 36,114,842.25 [28]. These high expenses highlight the need for evidence-based prescribing practices to control costs. Particularly, significant spending on low-evidence indications like SLE emphasises the necessity for such practices. Even though IVIG is expensive, it remains essential for treating conditions with few alternatives, such as primary immunodeficiency and CIDP [29]. However, recent evidence suggests that eltrombopag, a non-peptide thrombopoietin, might be more cost-effective than IVIG. Similarly, newer treatments like subcutaneous immunoglobulin and corticosteroids have been found to be as effective as IVIG, which was once the only effective treatment for CIDP [30]. Therefore, it is important to review and update IVIG prescribing guidelines based on the latest evidence.

To summarise, the present study highlights the importance of continuously reviewing and adhering to evidence-based guidelines for IVIG use, which involves assessing the cost-effectiveness of off-label uses and ensuring compliance with recommended dosing and infusion rates.

Limitation(s)

The present study was a single-centre study with a cross-sectional design and a limited sample size, which affects the generalisability of the study. Therefore, a prospective observational study would have helped to follow-up the patients for long run so that any adverse event would have been documented and a final diagnosis of the patients could have been reached.

CONCLUSION(S)

Majority of IVIG in the present study was prescribed for off-label use. A timely revision of IVIG use policy, as well as the establishment of a national IVIG prescribing guideline may provide standardisation in its usage, reduce cost burden, and encourage evidence-based prescribing of IVIG. Future research should address the limitations of this study, such as including outpatient IVIG use and extending the study duration, to improve the generalisability and applicability of the findings.

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- For any images presented appropriate consent has been obtained from the subjec. NA

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