

# Inpatient paediatric use of intravenous immunoglobulin at an academic medical centre

Dashti-Khavidaki S, Khalili H, Farshadi F, Aghamohammadi A, Movahedi M, Hajibabaei M

## ABSTRACT

**Introduction:** Intravenous immunoglobulin (IVIG) is an important research topic because of its efficacy in the management of an increasing number of diseases, its high cost and limited availability. This study was designed to evaluate the paediatric inpatient use of IVIG and identify strategies to reduce the drug expenditures.

**Methods:** Over a six-month period, physician and nursing charts, and notes for subjects who were treated with IVIG, were reviewed to gather the required data. This included patient demographics, IVIG, indications, dosage regimen, adverse drug reactions (ADRs) and their management.

**Results:** 58.3 percent of IVIG infusions were ordered for labelled indications. Patients in the labelled group experienced more clinical improvement than subjects in the off-label group. Haematologists and neurologists were the most prevalent prescribers. ADRs were more prevalent in the off-label group. Hypotension, fever, headache and chills were the most common adverse effects. ADRs were managed with drugs in 22.9 percent of IVIG administrations and IVIG infusions were modified in 12.5 percent of infusions.

**Conclusion:** ADRs were more prevalent in this hospital than those reported by other authors. This may be due to nursing negligence of the recommended infusion rate, higher sensitivity of our population or to the brands of IVIG which are used in the hospital. This shows the need for further evaluation of IVIG prescription and administration.

**Keywords:** adverse drug reactions, drug utilisation review, intravenous immunoglobulin

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## INTRODUCTION

Intravenous immunoglobulin (IVIG) is an important research topic in many medical centres because of its efficacy in the management of an increasing number of diseases, its high cost and limited availability.<sup>(1)</sup> IVIG products are used for a wide range of labelled and off-label indications. FDA-approved IVIG indications include primary immunodeficiency disease, idiopathic/immune-mediated thrombocytopenic purpura (ITP), human immunodeficiency virus, bone marrow transplantation, Kawasaki disease and chronic lymphocytic leukaemia. The off-label indications consist a wide range of autoimmune, allergic, and inflammatory disorders including Guillain-Barre syndrome, haemolytic anaemia, blistering mucocutaneous diseases.<sup>(2)</sup> There are also some investigational uses, without any controlled trial, for IVIG, such as intractable seizure.<sup>(3)</sup> IVIG dosage varies depending on the indication. Many institutions standardise IVIG administration protocols according to the manufacturer's recommendations and hospital policy for infusions. However, high-risk patients should be identified and managed appropriately.<sup>(4)</sup> This study was designed to evaluate the inpatient use of IVIG in Iranian paediatric patients and identify strategies to optimise drug administration and reduce drug expenditures.

## METHODS

Information on IVIG use was collected in an academic children's hospital. Over a six-month period, physician and nursing notes, and charts for subjects who were treated with IVIG, were reviewed to gather the following data: patient demographics (age, weight, gender), indication for IVIG administration, dosage regimen, adverse reactions and their prophylaxis or management. Indications were classified as labeled, off-label or investigational (with uncontrolled studies) uses of drugs.<sup>(2)</sup> This was an observational study without any intervention in the routine care of the subjects, and was approved by the local ethics committee.

## RESULTS

During the six-month period of research in this hospital, 48 courses of IVIG administration for 43 patients were recorded. More females than males were enrolled in this

Department of Clinical Pharmacy (Pharmacotherapy), School of Pharmacy, Tehran University of Medical Sciences, Poursina Ave, PO Box 14155/6451, Tehran 14174, Iran

Dashti-Khavidaki S, PharmD  
Assistant Professor

Khalili H, PharmD  
Assistant Professor

Farshadi F, PharmD  
Pharmacist

Hajibabaei M, PharmD  
Assistant Professor

Children Medical Center, Tehran University of Medical Sciences, Keshavarz Boulevard, Tehran 1419733151, Iran

Aghamohammadi A, MD  
Associate Professor

Movahedi M, MD  
Paediatrician and Associate Professor

Correspondence to:  
Dr Hossein Khalili  
Tel: (98) 912 297 9329  
Fax: (98) 21 664 61178  
Email: khalilih@sina.tums.ac.ir

study (53.4% versus 46.6%). IVIG was ordered to manage five different indications in these patients. 19 patients received IVIG for the management of ITP (39.6% of IVIG administrations), 11 patients for Guillain-Barre syndrome (22.9% of IVIG infusions), nine cases for Kawasaki disease (18.7% of IVIG administrations) and three subjects for intractable seizure. One of the patients was admitted six times to the hospital during this research period and he received IVIG at each admission. As a result, 16.7% of IVIG administrations were ordered to manage intractable seizure. One patient received IVIG for neonatal haemolytic anaemia (2.1% of IVIG administrations).

According to the above data, 28 (58.3%) of IVIG infusions were ordered for labelled indications, whereas off-label use accounted for 12 (25%) of IVIG administration, and investigational uses accounted for eight (16.7%) of IVIG administrations. In general, a higher dose of IVIG was administered to patients who received the product for a labelled indication (mean 19.8 g) compared to the dose administered for off-label (mean 14.9 g) or investigational purposes (mean 9.2 g). The average total dose was 1,380 mg/kg in the labelled group, 750 mg/kg in the off-label group, and 450 mg/kg in the investigational group. Overall, 85.7% of patients in the labelled group, 58.3% of the subjects in the off-label group and just 25% of cases in the investigational group experienced clinical improvement.

IVIG-induced adverse drug reactions (ADRs) occurred in 22 of 48 (45.8%) of the IVIG infusions. Adverse events were reported in 100% of the cases in the investigational group, 83.3% of the patients in the off-label group and 32.1% of the subjects in the labelled group. 37 ADRs were documented during these infusions, which translated into an ADR rate of 77%. Adverse reactions were classified as mild, moderate or severe, based on the classification introduced by other investigators.<sup>(5,6)</sup> Of the reported adverse effects, 48.7% were mild reactions, including fever (16.3%), headache (10.8%), chills (10.8%), myalgia (5.4%), nausea (2.7%), and abdominal pain (2.7%). 18.9% of ADRs were moderate in severity, including increased blood pressure (8.1%), urticaria (8.1%) and vomiting (2.7%). The only severe reported ADR was hypotension, with a rate of 32.4%.

13 of 37 ADRs (35.1%) occurred in patients who used this IVIG for labelled indications. Of these, 30.8% were mild, 15.4% were moderate and 53.8% were severe reactions. 20 of 37 ADRs (54%) observed in subjects received this drug for off-label purposes. 60% of ADRs in this group were mild, 25% were moderate, and 15% were severe reactions. Four of 37 (10.8%) of ADRs happened in patients who received this drug for an investigational indication; of these, 50% were mild and 50% were severe reactions. Decreased blood pressure (32.4%), fever (16.2%),

headache (10.8%) and chills (10.8%) were the most common adverse effects. Adverse events were managed with drugs, such as acetaminophen or non-steroidal anti-inflammatory drugs, in 11 (22.9%) of IVIG administrations. IVIG infusion rates were modified in nine administrations (18.8%) and temporarily stopped in three administrations (6.3%) due to the occurrence of adverse events. However, IVIG therapy was completed in the three patients after the adverse reactions resolved.

## DISCUSSION

The main aim of this study was to assess the clinical use of IVIG in paediatric inpatients who were treated with IVIG in the main academic children's hospital in Tehran, Iran. Overall, 58.3% of the study patients received IVIG therapy for labelled indications, 25% for off-label uses, and the remaining 16.7% for investigational indications. These findings showed that more than 50% of the IVIG administrations were for labelled indications in this hospital. Although ITP is considered as a labelled use of IVIG, prednisone is the first choice drug. In all subjects who received IVIG to manage ITP, this drug was selected as the first treatment of choice. Two of these patients (10.5%) failed to respond to IVIG and were controlled with prednisolone. According to the efficacy of prednisolone, treatment guidelines for ITP management, lower cost of prednisolone and its availability and ease of administration, ITP treatment in this hospital requires careful consideration. Similar to the findings of IVIG use by other researchers, haematologists and neurologists were the most prevalent prescribers (39.6% by each specialist).<sup>(7)</sup> The findings of this study showed that patients in the labelled group experienced more clinical improvements and less adverse effects than patients in the off-label and investigational groups. This result is compatible with the findings of other studies in academic hospitals of other countries.<sup>(1)</sup>

Although the adverse events reported in this study were mild or moderate in severity and were responsive to therapy, ADRs were more prevalent in this hospital than the ADR rates reported for IVIG use by other authors.<sup>(1,5,8)</sup> After changes in IVIG infusion regimens of six patients due to the occurrence of ADRs, three patients continued to complete the course of IVIG infusions; however, these events resulted in an increased length of hospital stay of at least one day. The higher prevalence of IVIG adverse events in these subjects may be due to nursing negligence of the recommended infusion rate, higher sensitivity of our population or due to brands of IVIG which are used in Iran. This indicates a need for further evaluation of IVIG prescription and administration in Iran. The limitation of this study is that only one academic hospital was evaluated. However, the important findings of the study show that

there is a need for further clinical research to evaluate the effectiveness of off-label or investigational use of IVIG, to compare IVIG products which are being used in hospitals, and to revise IVIG infusion protocols accordingly.

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