The shifting paradigm of clinical uses of immunoglobulin in the Paediatric Intensive Care Unit of a developing country

***Bandya Sahoo[1], Reshmi Mishra[1], Mukesh Kumar Jain[2], Sibabratta Patnaik[1]**

Sri Lanka Journal of Child Health, 2019; **48**(4): 334-337

Abstract

Background: Immunoglobulin is lifesaving and is the sole treatment option for certain diseases like primary immunodeficiencies. As it is an expensive therapeutic choice and has various potential harmful effects, its use should be carefully considered.

Objectives: To determine the changing pattern of intravenous immunoglobulin (IVIG) use based on level of evidence, clinical indications and adverse effects in a paediatric intensive care unit (PICU) of a developing country.

Method: The study was carried out in the PICU of Kalinga Institute of Medical Sciences over a period of six years. All children aged from 1 month to 14 years who received IVIG during their PICU stay were included.

Results: During the study period 61 children admitted to our PICU received IVIG for various indications. The use of IVIG in the low evidence category was as high as 41% in this study.

Conclusions: In this study IVIG was used in 41% patients who belonged to the low evidence category.

DOI: http://dx.doi.org/10.4038/sljch.v48i4.8828

(Key words: Immunoglobulin, changing, emerging, indications, level of evidence)

Introduction

Intravenous immunoglobulin (IVIG), whilst of benefit as replacement therapy in immunodeficiencies, has immunomodulatory and anti-inflammatory effects when used in higher doses in a variety of disorders[1]. Associated side effects include fever, headache, chills, myalgia, nausea and hypotension[2]. Moreover, considering its high cost, judicious use of this drug, particularly in resource limited settings, is of utmost importance. Several regulatory authorities have attempted to rationalize its use because of scarcity and cost. The United States Food and Drug Administration has approved the use of IVIG for only 6 clinical conditions[3].

Objective

To determine the changing pattern of intravenous immunoglobulin (IVIG) use based on level of evidence, clinical indications and adverse effects in a paediatric intensive care unit (PICU) of a developing country.

Method

This retrospective database review is an observational cohort study, carried out in the Paediatric Intensive Care Unit (PICU) of Kalinga Institute of Medical Sciences from 2013 to 2019 over a period of six years. Children prescribed IVIG whilst in the PICU were included in study. Demographic data, diagnosis, indications and dose of IVIG use, number of doses, side effects and outcome were collected on a structured data collection sheet. Approval for the study was obtained from the institutional ethics committee.

Results

During the period of six years, 61 patients received IVIG for various indications. Demographic and clinical characteristics of study group are shown in Table 1.

Neurological disorders comprised 15 children with Guillain Barre Syndrome (GBS), 9 with autoimmune encephalitis, 4 with acute disseminated encephalomyelitis, one with haemorrhagic leukoencehalopathy and one with viral encephalitis. Autoimmune disorders comprised 9 children with autoimmune encephalitis, 6 with Kawasaki disease, and one each with Kukichi Fuzimoto disease, systemic onset juvenile idiopathic arthritis and juvenile dermatomyositis. Haematological cases comprised 8 children with idiopathic thrombocytopenic purpura. All 7 cardiac cases had acute viral

[1]*Associate Professor,* [2]*Assistant Professor, Departmwnt of Paediatrics, Kalinga Institute of Medical Sciences, KIIT University, Odisha, India*
**Corresponding author:* bandyasahoo@gmail.com
orcid.org/ 0000-0002-2131-5728

(Received on 13 March 2019: Accepted after revision on 26 April 2019)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

myocarditis. Immunodeficiency disorders included one case of common variable immunodeficiency and two cases of secondary hemophagocytic lymphohistiocytosis. Infectious diseases included three cases with severe sepsis.

Table 1: ***Demographic and clinical characteristics of patients receiving IVIG (n=61)***

Characteristic	Number (%)
Gender	
Male	40 (65.6)
Female	21 (34.4)
Age	
1-12 months	11 (18.0)
13-59 months	26 (42.6)
6-14 years	24 (39.4)
Dose	
1mg/kg	
2mg/kg	
Number of doses	
1	43 (70.5)
2	03 (04.9)
More than 2	05 (08.2)
Missing data	10 (16.4)
Side effects	
Fever	02 (03.3)
Rash	01 (01.6)
Hypotension	01 (01.6)
Pain, swelling at site	01 (01.6)
Patient categories	
Neurological	30 (49.2)
Autoimmune	18 (29.5)
Haematology	08 (13.1)
Cardiac	07 (11.5)
Immunodeficiency	03 (04.9)
Infectious	03 (04.9)

The level of evidence was categorised as follows:[4]

Ia - Evidence from meta-analysis of randomised controlled trials

Ib - Evidence from at least one randomized controlled trial

IIa - Evidence from at least one controlled study without randomization

IIb - Evidence from at least one other type of quasi experimental study

III - Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies

IV- Evidence from expert committees' reports or opinions and/or clinical experience of respected authorities

Table 2 gives a summary of indications for use of IVIG in study based on prioritisation of treatment recommendations

Table2

Summary of indications for use of IVIG in study based on prioritisation of treatment recommendations

Degree of priority	No. of cases	Recommendation; level of evidence
Red (high priority)		
Guillain-Barre syndrome	15	Ia
Idiopathic thrombocytopenic purpura	08	Ia
Kawasaki disease	06	Ia
Primary immunodeficiency	01	IIb
Chronic inflammatory demyelinating polyneuropathy	01	I
Blue (medium priority)		
Paediatric myocarditis	07	III
Grey (low priority)		
Autoimmune encephalitis	09	IV
Acute disseminated encephalomyelitis	04	Ib
Systemic onset juvenile idiopathic arthritis	01	IV
Juvenile dermatomyositis	01	IIa
Unlisted diseases		
Bacterial Sepsis	03	III
Viral encephalitis	01	III
Haemorrhagic leukoencephalopathy	01	IV
Hemophagocytic lymphohistiocytosis	02	III
Kukichi Fuzimoto disease	01	IV

Indications for IVIG use belonged to evidence levels I and II in 59% of cases and levels III and IV in 41% of cases. (Table 2)

IVIG-induced adverse drug reactions occurred in 8 (13%) of the 61 IVIG infusions. This was managed by stopping the infusion and giving antipyretic and antihistamines whenever needed.

Dose and duration of therapy depended on the indication for IVIG administration. For neurological and autoimmune diseases a dose of 0.4 g/kg/day for five days was given. A dose of 2 g/kg/day in divided doses for five days was given for Kawasaki disease. In idiopathic thrombocytopenic purpura the dose used was 1 g/kg/day for two days.

Children with GBS took an average of three weeks to recover while autoimmune encephalitis patients took approximately two months to show reasonable resolution of symptoms. Most neurological patients had sequelae in the form of neurological disability. Mortality was recorded in three patients (5%).

Discussion

Greater than three fourths of IVIG in USA is prescribed for patients with autoimmune or inflammatory disorders[5]. In our retrospective review on the use of IVIG in patients admitted to our PICU over a six year period we found that 41% of IVIG administration was in the low evidence category. This is in contrast to the retrospective review conducted by Galal NM[6]. A recent study conducted in Pakistan by Jurair H et al has found a similar result to our study[7]. Use of IVIG beyond clear established indications has been seen worldwide. In adults IVIG has been used for non-listed indications in around 30–40%[8].

National Demand Management Programme of the UK Health Department formulated guidelines for IVIG use in England and Wales in 2008 and this was revised in 2011[9]. This guideline provides a colour coded classification of immunoglobulin indications in various diseases according to prioritisation. Red signifies a disorder where there is a risk to life without therapy. In our study 31 patients belonged to this category, GBS being the commonest indication. Although according to a study done by El-Bayoumi[10]. plasmapheresis was superior to IVIG in severe GBS, there is a practical hindrance for plasmapheresis. Blue signifies a disorder which is reasonably evidence based, but with other treatment options. Seven of our patients had blue indications. Grey signifies a disorder with no evidence for IVIG use. Diseases, not listed in the guidelines fall into the grey category. In our study 23 patients belonged to the grey category.

Newer indications for IVIG are based on strong clinical evidence. In our cohort, nine patients with autoimmune encephalitis were treated on strong clinical evidence. IVIG is indicated in patients with resistant dermatomyositis or aggressive disease[11]. Our patient with juvenile dermatomyositis did not respond to corticosteroids and therefore was treated with IVIG. Overall evidence, cost-effectiveness and risk of complications, should be assessed when IVIG is used to treat infection[12]. IVIG is indicated for necrotising PVL-associated staphylococcal sepsis after failure of all other therapies[9]. Among the three patients of sepsis in our study, one had severe staphylococcal sepsis and was treated with IVIG when other therapies failed. The patient with haemorrhagic leukoencephalitis received IVIG as there are no treatment guidelines, except for several case reports, which supported using IVIG[13]. To ensure optimal use of IVIG clinical guidelines for its use should be established based on locally available treatment options.

Conclusions

In this study IVIG was used in 41% of patients who belonged to the low evidence category.

References

1. Stiehm ER, Keller MA, Vyas GN. Preparation and use of therapeutic antibodies primarily of human origin. *Biologicals* 2008; **36**(6):363-74. https://doi.org/10.1016/j.biologicals.2008.07.002 PMid:18789721

2. Brennan VM, Salomé-Bentley NJ, Chapel HM. Immunology Nurses Study. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. *Clinical and Experimental Immunology* 2003; **133**:247-51. https://doi.org/10.1046/j.13652249.2003.02199.x PMid:12869031 PMCid:PMC1808773

3. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the primary immunodeficiency committee of the American Academy of Allergy, Asthma and Immunology. *Journal of Allergy and*

Clinical Immunology 2006; **117**: S525-S553.
https://doi.org/10.1016/j.jaci.2006.01.015
PMid: 16580469

4. General Guidelines for methodologies on research and evaluation of traditional medicine. Levels of Evidence. Available from:
http://apps.who.int/medicinedocs/en/d/Jwhozip42e/13.1.html

5. Gelfand EW. Intravenous immune globulin in autoimmune andinflammatory diseases. *New England Journal of Medicine* 2012; **367**:2015-25.
https://doi.org/10.1056/NEJMra1009433
PMid:23171098

6. Galal NM. Pattern of intravenous immunoglobulins (IVIG) use in a paediatric intensive care facility in a resource limited setting. *African Health Sciences* 2013; **13**(2):261-5.
PMid: 24235922 PMCid: PMC3824471

7. Jurair H, Shabir A, Hussain K, Qalab-e-Abbas, Anwar-ul-Haque. Intravenous immunoglobulin use in paediatric intensive care unit of a developing country. *Journal of Paediatric Critical Care* 2016; **3**(1):7-10.
https://doi.org/10.21304/2016.0301.00102

8. Wu J, Lee AJ, Goh AE, Chia M, Ho C, Bugarin JL, *et al.* Use of intravenous immunoglobulin in an Asian paediatric population over a 10-year period. *Journal of Paediatrics and Child Health* 2013; **49**(8):629-34.
https://doi.org/10.1111/jpc.12262
PMid: 23750995

9. Department of Health. Clinical Guidelines for Immunoglobulin Use: Second Edition Update. July 2011.
http://www.ivig.nhs.uk/documents/dh_129666.

10. El-Bayoumi MA, El-Refaey AM, Abdelkader AM, El-Assmy MM, Alwakeel AA, El-Tahan HM. Comparison of intravenous immunoglobulin and plasma exchange in treatment of mechanically ventilated children with Guillain Barré syndrome: a randomized study. *Critical Care* 2011;**15**(4):R164.
https://doi.org/10.1186/cc10305
PMid: 21745374 PMCid: PMC3387601

11. Enk A. Guidelines on the use of high-dose intravenous immunoglobulin in dermatology. *European Journal of Dermatology* 2009; **19**(1):90-8.
PMid: 19171549

12. Soares M, Welton N, Harrison D, Peura P, Hari M, Harvey S, et al. An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis. *Health Technology Assessment* 2012; **16**(7):1-186.
https://doi.org/10.3310/hta16070
PMCid: PMC4781633

13. Khademi GR, Aelami MH. Acute hemorrhagic leukoencephalitis in children: a case report. Iran Journal of Medical Sciences 2016; **41**(3):245-8.
PMid: 27217610