Study of use of intravenous immunoglobulin in pediatric intensive care unit in a tertiary care center: An audit and review of evidence

Maaz Ahmed, M. L. Keshavamurthy, K. S. Sanjay, Raghavendra Gumur, G. V. Basavaraja
Department of Pediatric Medicine, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India

Abstract

Introduction: The label and off-label use of intravenous immunoglobulin (IVIG) in pediatric intensive care unit (PICU) is done as a replacement therapy also for immunomodulation. As there are no standard guidelines for the use of IVIG in PICU; hence, the need to study the pattern of indications for which IVIG has been used in critically ill children and review the quality of evidence as per the available data.

Materials and Methods: The retrospective chart review of indications for IVIG therapy in children over a period of 4 years in a tertiary care PICU from January 2015 to December 2018. Collection of data included demographic profile, indication of transfusion of IVIG, dose of IVIG received, and outcome of the patients.

Results: The IVIG therapy was given to 301 children under the following groups, 120 children for neuroimmunologic disorders, 73 children for cardiology-related indications, 65 children for infection and infection-related causes, 31 children for autoimmune diseases, seven and five children each for primary immunodeficiency and dermatological causes, respectively. The indications, for which IVIG therapy given included, approved by the Food and Drug Administration in 56 children, under evidence category Level Ia in 50 children and with strength of recommendation Grade A in 51 children.

Conclusion: There is a rise in off-label use of IVIG as the quality of evidence is variable for different indications hence there is a need for better quality of evidence and more multicentric randomized control trials to define the precise impact of IVIG on various conditions.

Keywords: Critically ill children, intravenous immunoglobulin, off-label

INTRODUCTION

The use of intravenous immunoglobulin (IVIG) for array of clinical conditions has been ever increasing. The United States Food and Drug Administration (FDA) has approved the use of IVIG in six conditions only. The IVIG is used as a source to replace antibodies at dose of 200–400 mg/kg/month in conditions with primary and secondary antibody deficiencies. At a higher dose of 2 g/kg, IVIG serves as immunomodulatory and anti-inflammatory agent, through mechanisms...
such as autoantibody neutralization and production of interleukin-12.[2-5] Apart from FDA, the American Academy of Allergy and Immunology, the Canadian Agency for Drugs and Technologies in Health, and Comité d’ évaluation et de diffusion des innovation technologies have scientifically evaluated the available evidence on the use of immunoglobulin and come out with recommendations of its appropriate use.[1,2,3,4] The aim of the study is to review the pattern of use IVIG therapy in critically ill children in pediatric intensive care unit (PICU) setting and assess the quality of evidence for off-label indications of transfusion.

MATERIALS AND METHODS

The study was conducted over a period of 4 years in a tertiary care PICU from January 2015 to December 2018. It is a retrospective chart review of IVIG transfusion received by the children in a 35-bed PICU. The study was conducted after approval of institutional ethics committee.

The study included patients who had received one or more doses of IVIG transfusion from the age of 1 month to 18 years. The demographic profile, indication of transfusion of IVIG, dose of IVIG received, length of stay, and outcome of the each patient were collected. If the primary indication was not clearly stated in the medical records, then the final diagnosis or a significant clinical finding that was recorded prior to the administration of IVIG was taken to be primary indication of transfusion of IVIG. The indication of IVIG was categorized as, unknown, if the above mentioned was not observed during the analysis of records.

Statistical analysis

Categorical was represented as frequencies, proportions, and percentages. The continuous data were analyzed as standard deviation or means or medians or interquartile ranges if data were found to be skewed.

RESULTS

Three hundred and one cases received IVIG therapy during the 4-year study with median age of 5 years and 61.4% (185) children were being males. The patients transfused IVIG under the following clinical categories, 120 cases with neuroimmunologic disorders; 73 cases with cardiology-related indications; 65 children with infection and infection-related cases; 31 with autoimmune diseases (hematological); seven children with primary immunodeficiency; and five with dermatology-related causes.

Fifty-six (18.6%) cases who received IVIG were of FDA approved indications which included (primary immune deficiency, idiopathic thrombocytopenic purpura [ITP], and Kawasaki disease).

The diagnosis at admission was ITP in 31 cases, acute myocarditis in 72 cases and one case with dilated cardiomypathy (DCM). All five cases of dermatological diseases were toxic epidermal necrolysis (TEN). Among infection-related diseases, 19 cases with Kawasaki disease, 45 cases with sepsis syndrome, and one case was diagnosed as toxic shock syndrome. Ninety-six cases with Guillain–Barré syndrome (GBS) while other neurological cases were as follows, 10 cases with super-refractory status epilepticus (SRSE), five cases with autoimmune encephalitis, four cases with acute disseminated encephalomyelitis (ADEM), two cases with acute necrotizing encephalopathy (ANEC), and one case each with myasthenia gravis, acute transverse myelitis, and acute flaccid myelitis. Among the primary immunodeficiency disease, two cases with Bruton’s Agammaglobulinemia, four cases with severe combined immunodeficiency (SCID), and one case with Selective IgA deficiency were transfused IVIG.

As per the review of evidence [Table 1] by workgroup report of the American Academy of Allergy, Asthma, and Immunology the indications have been classified further. About 50% cases (152 cases) received IVIG with definitely beneficial category, 30% (91 cases) it may provide benefit category, seven in probably beneficial category and two cases in unlikely to provide benefit category which include DCM and Selective IgA deficiency.

Under evidence categories, Level Ia category included 50 cases, category Level Ib included 99 cases, five cases in Level IIa category, nine cases in Level IIb category, 88 cases in Level III category, and one case of selective IgA deficiency in Level IV category.

The summary of evidence for indications for which intravenous immunoglobulin that was used as per American academy of allergy and immunology has been shown in Table 2.

With respect to strength of recommendation classification of indications, Grade A had 51 cases, Grade B included 63 cases, Grade C included 137 cases, and Grade D included one case. Four indications not classified include sepsis syndrome, acute transverse myelitis, ANEC, and acute flaccid myelitis but there available evidence has been discussed subsequently.
Outcome measures

Mortality was seen in 16.9% children (21 cases of acute myocarditis, 13 cases of Sepsis syndrome, seven cases of GBS, three cases of SRSE, two cases of TEN, one case each of agammaglobulinemia, ANEC, SCID, Toxic shock syndrome, and one Selective Ig A deficiency.

DISCUSSION

We critically reviewed, in keeping currently available evidence, label and off-label indications for which IVIG therapy had been used in 301 critically ill children in PICU. Fifty-six children received IVIG for indications that are FDA approved; 50 children were transfused IVIG for indications that were in evidence category Level Ia and 51 children for indications with a strength of recommendation of grade A. There is a rise in off-label use of IVIG but the quality of evidence is variable for various indications.

Adjuvant therapy of IVIG in 45 children with bacterial sepsis or septic shock was given due to possible bactericidal mechanisms such as opsonization of antibodies, stimulation of phagocytosis, and neutralization of toxins of bacteria.[6-8] A prospective randomized control trial involving IVIG in sepsis syndrome in children in PICU demonstrated a significant reduction in mortality and length of stay.[9] However, a Cochrane review in which 43 trials were included, demonstrated that polyclonal IVIG was not associated with reduced mortality in neonates or adults in sepsis.[10] Other uses of IVIG that had been studied include postoperative sepsis[11] and trauma-associated sepsis.[12] The use of IVIG therapy in setting of sepsis necessitates more specific definition.

The pro-inflammatory cytokine storm caused by endotoxin or super antigen-activated blood cells may be suppressed by IVIG,[4] hence its use in condition such as streptococcal toxic shock, whereas in our study, we observed only one case with toxic shock syndrome that was given IVIG therapy, succumbed to the disease.[13-16]

Since several multicenter randomized trials demonstrated the efficiency of high-dose IVIG in comparison with systemic steroids in raising platelets in ITP which led to FDA approval as well as its use in prevention and control of bleeding in severe forms, support the rationale of the use of IVIG in 31 children in our PICU.[2,17-20]

Seventy-two children received IVIG in cases with acute myocarditis including 15 cases secondary to dengue and overall 21% mortality though our diagnosis was based on clinical, laboratory, and 2D echo for diagnosis but follow-up 2D echo could not done in most cases. Although IVIG was found to be beneficial only in case reports with myocarditis.[21,22] Only one case of recent onset DCM received IVIG in our study. A case series of 17 patients showed decrease in parvovirus B19 load and improvement in ejection fraction[23] but no benefit of improvement of ejection fraction was seen with cases receiving IVIG over placebo as observed in a prospective, placebo-controlled trial.[14]

As per the accepted standard of care, all 19 cases of Kawasaki Disease received IVIG, in combination with aspirin, within 10 days of the syndrome with the purpose of the prevention of aneurysm in coronaries.[24-27] The meta-analysis of data of more than 3400 children who were given single high-dose IVIG has been shown to more effective in prevention coronary aneurysms.[28]

Among the five cases of TEN, three survived and mean length of stay in survival group was 11 days and those not survived was mean of 20 days which was similar to large retrospective study of 65 patients but results of the study was statistically not significant.[29] Seventeen studies with the use of IVIG in TEN was analyzed in a systematic review and meta-analysis showed an insignificant reduction in mortality thus there is a need for more large scale randomized control trials (RCTs) of IVIG in TEN.[30]

All 96 cases of GBS were treated with IVIG irrespective of whether they were on ventilator or not and none of them underwent plasma exchange as it was not available at our center. A Cochrane review had concluded that if IVIG is given in severe disease within 14 days form onset, speedy recovery is as same as in plasma exchange also IVIG therapy was better than supportive care alone.[31] One systematic review showed, for ventilated patients plasma exchange was better.[32] Another systematic review gave mixed results with the treatment of IVIG with pediatric GBS but concluded that when compared to plasma exchange or supportive care, IVIG was a possible treatment option.[33]

There are multiple reasons of off-label use of IVIG in various neurological conditions. The IVIG therapy has the ability to affect remyelination directly, generate antiidiotype antibodies, modulate T cells and macrophages, suppress pathogenic cytokines and inhibit the complement pathway.[34] The IVIG was used in four cases of ADEM which were steroid-resistant. A systematic review based on case reports and case series concluded that IVIG to be possible treatment with steroid-resistant ADEM.[35,36] Although positive and successful IVIG exists more large-scale investigations are required.
Ten cases of SRSE in the study received immunotherapy in the form of high-dose steroids followed by IVIG, as autoimmune cause was considered as cause for refractory status epilepticus. If the SRSE is due to autoimmune etiology then prompt treatment with immunotherapy is warranted but if the diagnosis is less certain then IVIG therapy can be considered. In a retrospective study of 17 pediatric patients by Arayakarnkul and Chomtho who were diagnosed with SRSE most common cause was immune-mediated encephalitis. IVIG was given in 8 cases which did not result in immediate control of seizures but a slow overall improvement was noted.

In the study, five cases of autoimmune encephalitis received IVIG. Three systematic reviews reported insufficient evidence for the use of IVIG in the treatment of autoimmune encephalitis, while one meta-analysis concluded that placebo or IVIG with respect to disability outcomes had no difference, but one systematic review had positive reports for IVIG.

Two cases of ANEC were treated with IVIG post steroid therapy as ANEC is also considered due to “cytokine storm” or hypercytokinemia as an exaggerated response to several viral pathogens though no studies show evidence. One case of acute transverse myelitis IVIG was given since it is a demyelinating disease with autoantibodies. The use of IVIG in transverse myelitis as against standard therapy was studied in a multicenter, randomized control trial in adult as well as pediatric patients but they found no difference in the trial arms.

In one case of exacerbation of myasthenia gravis IVIG was given. Two RCTs did not demonstrate significant difference between IVIG and plasma exchange and one RCT of IVIG versus placebo demonstrated some evidence of effectiveness of IVIG. In one systematic review reported improvement of MG with IVIG but three systematic reviews concluded that among IVIG, plasma exchange and placebo, none were better.

One case with selective IgA deficiency IVIG was given without determining whether there was IgG2 subclass deficiency due to financial constraints, thus it was not indicated. However, if there was poor production of IgG antibody and specific subclass IgG2 deficiency then immunoglobulin replacement therapy can be given.

Limitations of the study include being a retrospective study and no control group to analyze the effectiveness of IVIG in various conditions.

Table 1: The evidence category, strength of recommendation and ordinal category

| Number | Definition |
|--------|------------|
| Evidence category | From meta-analysis of RCTs |
| Ia | From at least one RCT |
| Ib | From at least one controlled trial without randomization |
| Iia | From at least one other type of quasi-experimental study |
| IIb | From nonexperimental descriptive study like, case-control study |
| III | Not rated |

| Strength of recommendation | Based on category I evidence |
|---------------------------|-----------------------------|
| A | Based on category II evidence |
| B | Based on category III evidence |
| C | Not rated |

| Ordinal category | Definitely beneficial |
|-----------------|----------------------|
| May provide benefit |
| Unlikely to provide benefit |

RCTs: Randomized control trials, NR: Not rated

Table 2: Summary of evidence for indications for which intravenous immunoglobulin was used as per American academy of allergy and immunology

| System | Indication | n (%) | FDA | Evidence category | Strength of recommendation | Benefit |
|--------|------------|-------|-----|-------------------|---------------------------|---------|
| Neuro-immunological | GBS | 96 (31.8) | No | Ib | A | Probably beneficial |
| | FIRES | 10 (3) | No | III | C | May provide benefit |
| | Autoimmune encephalitis | 10 (3) | No | III | C | May provide benefit |
| | ADEM | 4 (1.3) | No | IIb | C | May provide benefit |
| | Myasthenia gravis | 1 (0.35) | No | Ib | B | Probably beneficial |
| Infection related diseases | Kawasaki disease | 19 (6.3) | Yes | Ib | A | Definitely beneficial |
| | Toxic shock syndrome | 1 (0.35) | No | III | C | May provide benefit |
| Hematologic autoimmune | ITP | 31 (10.2) | Yes | Ib | A | Definitely beneficial |
| Cardiology | Acute myocarditis | 72 (23.9) | No | III | C | May provide benefit |
| | DCM | 1 (0.35) | No | Ib | A | Unlikely to be beneficial |
| Dermatological | TEN | 5 (1.6) | No | III | C | May provide benefit |
| Primary and secondary | Bruton’s Agammaglobulinemia | 2 (0.6) | Yes | IIb | B | Definitely beneficial |
| immune deficiencies | Selective immunoglobulin A deficiency | 1 (0.35) | Yes | IV | D | Unlikely to be beneficial |
| | SCID | 4 (1.3) | Yes | IIb | B | Definitely beneficial |

GBS: Guillain-Barré syndrome, SCID: Severe combined immunodeficiency, TEN: Toxic Epidermal necrolysis, ADEM: Acute Disseminated Encephalomyelitis, DCM: Dilated Cardiomyopathy, ITP: Idiopathic thrombocytopenic purpura, FDA: Food and Drug Administration
CONCLUSION

IVIG is still being used off-label in many conditions but there is a need for better quality of evidence and more RCTs to define the impact of IVIG on various conditions.

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Conflicts of interest
There are no conflicts of interest.

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