Use of intravenous immunoglobulin in pediatric practice

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Abstract

In recent years, human-driven intravenous immunoglobulins (IVIG) administered intravenously have been widely used in treatment of many diseases. Intravenous immunoglobulin is obtained from human-driven plasma pools as in other plasma-driven products and IVIG preparations contain structurally and functionally intact immunoglobulin. Intravenous immunoglobulin was approved by FDA (Food and Drug Administration) in USA in 1981 for the first time and was started to be primarily used in patients with immune deficiency with hypogammaglobulinemia. The effects of intravenous immunoglobulin include complex mechanisms, but it exerts its essential action by eliminating the non-specific Fc receptors found in the mononuclear phagocytic system or by inhibiting binding of immune complexes to Fc receptors in the cells. Their areas of usage include conditions where their anti-inflammatory and immunomodulator effects are utilized in addition to replacement of deficient immunoglobulin. Although the definite indications are limited, it has been shown that it is useful in many diseases in clinical practice. Its side effects include fever, sweating, nausea, tachycardia, eczematous reactions, aseptic meningitis, renal failure and hematological-thromboembolic events. In this article, use of IVIG, its mechanisms of action, indications and side effects were discussed. (Türk Ped Arş 2014; 49: 282-8)

Key words: Child, hypogammaglobulinemia, intravenous immunoglobulin

Introduction

In recent years, human-driven intravenous immunoglobulins (IVIG) have been more widely used for treatment of many diseases. Although the main aim is to replace the deficient immunoglobulin, they have been shown to be efficient in treatment of many diseases with their anti-inflammatory and immunomodulator effects. Intravenous immunoglobulin was approved by Food and Drug Administration (FDA) in 1981 for the first time in USA and was started to be used in patients with immunodeficiency characterized hypogammaglobulinemia (1). Its consumption increased in time

with widening of its area of usage. Hence, it has been consumed with a 2,5-fold higher rate in the last 15 years in Europe, while the amount of IVIG imported and consumed continues to increase. In our article, the areas of usage, mechanisms of action and side effects of IVIG which has been used frequently in pediatric practice are mentioned.

Mechanism of action

The effects of intravenous immunoglobulin include complex mechanisms. It shows its main action by eliminating non-specific Fc receptors found in the mononuclear phagocytic system or inhibiting binding of im-

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munocomplexes to the Fc receptors on cells. Other mechanisms of action include interaction with complement and cytokines, anti-idiotypic property, decrease in the action of dendritic cells and T and B cell activation and differentiation (2-5).

1) Fc receptor-mediated action

Fc receptors which are found in most of the hematopoietic cells (macrophages, dendritic cells, microglia and neutrophils) act as activators and inhibitors. The fatal effects of these cells are reduced by decreasing receptor-mediated cytokine and other proinflammatory mediator release from the macrophages.

2) T cell mediated action

T cells play an important role on the adaptive immune system. Intravenous immunoglobulins cause to programmed T cell inactivation and/or death.

3) Action on B cells

Many autoimmune diseases occur because of autoantibodies released from B cells. Intravenous immunoglobulin acts on B cells with different ways. It causes to down-regulation of the antibodies formed by B cells. It neutralizes pathogenic antibodies, since it includes many anti-idiotypes (anti-FVIII, anti-DNA, anti-tyroglobulin, anti-neuroblastoma, anti-laminin). It inhibits B cell growth by blocking some receptors on B cells. It inhibits release of autoantibodies from B cells with its anti-CD5 content. It contributes to pathological autoantibody catabolism. It realizes this by FcRn receptor which plays in IgG catabolism. It neutralizes BAFF-B cell activating factor which provides B cell differentiation.

4) Action on dendritic cells

Dendritic cells are thought to be responsible of primary immune response, since they are involved in immature T cell activation. High dose IVIG which is given to lupus patients inhibits expression of CD80/86 and Human Leukocyte Antigen (HLA) (efficient in antigen presentation and T cell activation) by inhibiting dendritic cell differentiation.

5) Action on cytokine production

Interferon (IFN)-gamma, interleukin (IL)-4 and IL-5 which are proinflammatory/antiinflammatory cytokines are released from activated Th1 and Th2 cells. The balance between these cells are disturbed in autoimmune diseases and Th1 derived cytokines become

predominant. Since intravenous immunoglobulins include antibodies against Th1 cytokines, they help in elimination of this imbalance.

6) Action on the complement system

They inhibit activation by binding to C3b and C4b in the complement system.

7) Intravenous immunoglobulins inhibit B cell

functions by behaving like antiidiotypic antibodies

An ideal IVIG preparation: The number of donors should be more than 4000 (5000-10000), the half-life should be longer than 20 days, the monomeric IgG should be higher than 90%, IgG subgroup distribution should be appropriate and Fc functions should be complete (complement binding and opsonization), it should not include pyrogenic substances, aggregates or vasoactive substances, it should have few side effects, it should include minimal IgA, it should be sterile, regular and stable and should be easily soluble if it is powder and it should be inexpensive (6). In Table 1, the properties of some IVIG preparations found in Turkey are shown.

Side effects

Side effects against intravenous immunoglobulin products have been reported with a rate of 20% (7). Although most of these side effects are minor and transient, severe side effects are observed with a rate of 2-6% (8). The side effects can be examined under the titles of immediate, delayed and late side effects (9).

1) Immediate side effects: They occur in 6 hours after the beginning of infusion.

- Pain, swelling, erythema at the site of infusion
- Head pain, nausea, vomiting
- Myalgia, back pain, arthralgia
- Fever, sweating, erythema in the face, hypo/hypertension, tachycardia
- Anaphylactic/anaphylactoid reaction
- Anxiety, fatigue
- Anaphylaxis in patients with IgA deficiency: Although it is thought to be related with anti-IgA antibodies found in the structure of IgG and IgE, it is still controversial. Therefore, IgA preparations with lower IgA content should be preferred in these patients (10). Subcutaneous IVIG can be used, if allergic reaction develops despite use of preparations with low IgA content (11).

Table 1. Intravenous immunoglobulin preparations

Name	Company	Preparation	Stabilizer procedure	Antimicrobial procedure	Amount of IgA (microgram/mL)
Octagram	Octapharma	5% liquid	Maltose	Solvent-detergent Low pH	100
Flebogamma	Grifols	5%, 10% liquid	D-sorbitol	Cold ethanol fraction, ion exchange, chromatography, low pH, solvent-detergent, nanofiltration	5% <50 10% <100
Tegelin	Er-kim	Lyophilized	Sucrose	Cohn-Onclay fraction, deep filtration, ultrafiltration, nanofiltration, low pH pepsin application	17
Gamunex	Biem	Liquid	Glycine	Caprylate/chromatography	0.046 mg/dL
Kiovig	Baxter	Lyophilized	Glycine	Cohn-Onclay cold ethanol fraction, solvent/detergent (S/D), nanofiltration (35 nm), incubation at low pH and high temperature, pasteurization (21-23 days)	<0.14 mg/mL
Ig vena	Onco drug	Liquid	Maltose	Solvent-detergent	<0.05 mg

PEG: percutaneous endoscopic gastrostomy

2) Delayed side effects: these side effects develop in 6 hours-1 week.

a) Neurological side effects: Neurological side effects include migraine like headache and aseptic meningitis. Nausea, vomiting, photophobia and muscle cramps may accompany headache. Some headache types are resistant and very severe and nuchal rigidity and fever may also accompany pain. In this situation, pleocytosis is observed in cerebrospinal fluid when lumbar puncture is performed and the picture is called aseptic meningitis. Aseptic meningitis has been mostly related with high dose IVIG useage (9).

b) Thromboembolic complications: Coronary artery disease, cerebrovascular disease, previous embolic attack, smoking, hypertension, diabetes, hyperlipidemia are risk factors for thromboembolism. In addition, hereditary thrombophilia, catheter, autoimmunity, estrogen use in advanced age and immobilization are also among the risk factors. These complications are generally observed after administration of a high dose and rapid infusion. Thromboembolis events raging from regional thromboembolic event to acute myocardial infarction, coronary syndrome, stroke and deep vein thrombosis (9, 12, 13).

c) Nephrological side effects: Acute renal failure, hyponatremia and pseudohyponatremia are the main nephrological side effects. Acute renal failure related with intravenous immunoglobulin usage is observed in less than 1% of the subjects (14). It may be man-

ifested with different clinical pictures ranging from asymptomatic creatinine elevation to anuric renal failure. It is generally observed following use of high dose IVIG and spontaneously improves in 4-10 days. It is thought that renal failure develops as a result of sucrose which is found in IVIG preparations and can not be metabolized and which accumulates in the tubules as a result of tubular reabsorption leading to obstruction (7-9).

Actual hyponatremia which develops following administration of intravenous immunoglobulin is thought to be related with sucrose and free water load found inside the product. Sucrose causes to hyponatremia by providing fluid passage from the intravascular area into the extravascular area and free water causes to hyponatremia by creating water load mostly in individuals with tubular damage (15).

Pseudohyponatremia develops in relation with protein and lipids found in IVIG (15).

d) Hematological side effects: Positive Coomb's test, hemolytic anemia and neutropenia are among the hematological side effects caused by use of IVIG. In many patients, subclinical mild Coomb's positivity has been reported. However, Coomb's positive hemolytic anemias leading to clinically severe hemolysis have also been reported. It is thought that hemolytic anemia is related with erythrocyte alloantibodies (anti-A, anti-B and anti-D) found in IVIG preparation (16-18).

Table 2. Areas of usage of intravenous immunoglobulin*

Primary indications	Hematological diseases
Alloimmune thrombocytopenia	Chronic ITP
Chronic inflammatory demyelinating polyradiculopathy	Acquired aplastic anemia (non-parvovirus-related)
Gullian-Barre syndrome	Aplastic anemia/pancytopenia
Neonatal hemolytic disease	Autoimmune neutropenia
Primary immune deficiency	Neurological diseases
Congenital hypothyroidism in primary immune deficiency	Acquired diffuse encephalomyelitis unresponsive to high dose steroid
ITP (acute and persistent)	Autoimmune encephalitis
Kawasaki disease	Complex regional pain syndrome
Paraprotein-related demyelinating neuropathy	Neuromyotonia
Toxic epidermal necrosis, Steven-Johnson syndrome	Resistant childhood epilepsy
Secondary indications	Opsoclonus, myoclonus
Acquired erythroid aplasia	Acute idiopathic disautonomia
Autoimmune congenital heart block	Chronic facial pain
Autoimmune hemolytic anemia	Diabetic proximal neuropathy
Autoimmune uveitis	Infectious diseases
Presence of coagulation factor inhibitors	In prophylactic treatment for viral or pathogenic infections in cases where intramuscular injection is contraindicated or hyperimmunoglobulin can not be found
Hemophagocytic syndromes	Pyoderma gangrenosum
Immunobullous diseases	Other
Inflammatory neuropathy	Urticaria (severe/resistant)
Multifocal motor neuropathy	Atopic dermatitis/eczema
Myasthenia gravis (including Lambert-Eaton)	Hemolytic uremic syndrome
Necrotizing staphylococcal sepsis	Non-T/B cell-related paraneoplastic syndromes
Posttransfusion purpura	Diseases for which there is no proof for use of IVIG
Rasmussen syndrome	Immune deficiency related with childhood HIV infection
Secondary antibody deficiency	Adrenoleukodystrophy
Severe and recurrent Clostridium difficile colitis	Alzheimer disease
Staphylococcal or streptococcal toxic shock syndrome	Amyotrophic lateral sclerosis
Stiff-Person syndrome	Chronic fatigue syndrome
Solid organ transplantation	Critical neuropathic disease
Tertiary indications	Multiple sclerosis
Rheumatic diseases	Rheumatic arthritis
Severe antiphospholipid syndrome	Neonatal sepsis (for treatment and prophylaxis)
Antiphospholipid antibody-related brain infarction	Specific infection or non-C.difficile-related intensive care sepsis
Central nervous system vasculitis	Asthma
Systemic juvenile idiopathic arthritis	Graves ophthalmopathy
Systemic vasculitis and ANCA(+) diseases	Unsuccessful in vitro fertilization
PANDAS	Recurrent pregnancy losses
SLE (non-secondary immune cytopenia-related)	

*Adapted from Demand management plan for IVIG use 2012 (Dept. Health London).

ITP: immune thrombocytopenic purpura; ANCA: anti-neutrophil cytoplasmic antibody; PANDAS: pediatric autoimmune neuropsychiatric diagnosis associated with streptococcal infections; SLE: systemic lupus erythematosus; HIV: human immunodeficiency virus

Transient neutropenias may be observed in relation with use of intravenous immunoglobulin. It is thought that this may be related with immunoglobulin or complement-mediated neutrophil activation and neutrophil activation or migration which develops as a result of increased adhesion molecules. On the other hand, it is also thought that anti-neutrophil antibody or celiac acid binding immunoglobulin-like lectin-9-Siglec-9 may lead to neutropenia (19-21).

e) Dermatological side effects: Dishydrosis (small vesicles on the hands and feet) and eczematous reactions may be observed following use of intravenous immunoglobulin. Generally, good response is obtained with topical steroids (22).

f) Side effects related with the lung: Dyspnea and wheezing are observed more frequently, but severe side effects including pulmonary emboly, pulmonary edema, pleuresia and transfusion related lung disease are also reported (23-25).

3) Late reactions: These are the side effects which are observed weeks-months after intravenous immunoglobulin usage.

- Passive antiviral and antibacterial antibodies which are transferred by intravenous immunoglobulin affect the serological results and inhibit response to vaccines. Therefore, IDSA (Infectious Diseases Society of America) 2013 guideline recommends live viral vaccines to be administered 8 months after administration of low dose (400 mg/kg) IVIG and 11 months after administration of high dose (2 g/kg) IVIG (26).
- Transmission of viruses including hepatitis B virus (HBV), Human immune deficiency virus (HIV) and hepatitis C virus (HCV) has been very rarely reported with administration of immunoglobulins (2). No transmission of prions has been reported so far. In order to prevent these transmissions, selection of plasma donors should be made carefully, all known viral agents should be screened with polymerase chain reaction (PCR) and transaminases should be checked not to miss the window period of viral infections. Even if these procedures have been fulfilled, the donor's plasma should be kept until a plasma sample is obtained from the same donor and

tested and should be used only if the tests belonging to the second sample are negative. All manufacturer institutions should additionally perform complementary purifying and virucidal procedures (especially precipitation with ethanol, fatty acid treatment, deep filtration, chromatography, solvent/detergent treatment for enveloped viruses and viral filtration for non-enveloped viruses). Even if it is considered that IVIG produced by these purifying procedures does not contain pathogens, patients who receive IVIG should be closely followed up in terms of the possibility of many unknown viruses/prions (27).

Areas of usage

Intravenous immunoglobulin is used for replacement in immunodeficiencies and as immunomodulator in autoimmune/systemic diseases. Although the absolute indications of intravenous immunoglobulin are limited, it has been clinically shown to be beneficial in many diseases (28).

1) Replacement treatment

a) It is generally administered at a dose of 400-500 mg/kg every 3-4 weeks for prophylaxis against recurrent infections in primary immune deficiencies (6, 29, 30).

b) In secondary immune deficiencies (chronic lymphoid leukemia, multiple myeloma), it is used at a similar dose and frequency to decrease the risk of severe and recurrent infections which would develop in relation with decreased antibody production (31).

c) In acquired immune deficiency in the childhood: It may be used at a dose of 0.2-0.4 g/kg every 4 weeks for treatment in opportunistic infections related with hypogammaglobulinemia, recurrent bacterial infections and/or inefficient antibiotic and antiretroviral treatment in HIV positive children (29, 30).

2) Immunomodulator

High dose IVIG acts as an antiinflammatory agent and inhibits the immune system. Due to this action, it is used in autoimmune and/or inflammatory diseases, hematologic, rheumatic and neurological diseases.

a) Immune thrombocytopenic purpura (ITP): In hemorrhagic ITP and in patients who are being prepared for surgical intervention, IVIG can be used at a dose of 1 g/kg/day for two days or 0.4 g/kg/day for five days (6, 28, 32).

b) Kawasaki disease: Here, it is recommended to be used at a dose of 2 g/kg for a single day or in divided doses in five days. Administration in divided doses in five days has been shown to be more efficient in preventing coronary artery aneurism. Acetylsalicylic acid is used in addition to IVIG for treatment of this disease (28, 30, 33).

c) Guillain-Barre Syndrome: Recovery is observed in two weeks with use of IVIG. IVIG at a dose of 1 g/kg/day or 0.5 g/kg/day for five days can be used for treatment (28, 34).

There are also other diseases for which IVIG is used in addition to the above mentioned diseases and these are shown in Table 2.

Conclusively, intravenous immunoglobulins which have definite and partial indications at different times and doses in almost all areas of medicine for more than 40 years and which are the main biological products are being used more frequently in our country and in the whole world with the development of plasma industry. There are no common, definite and severe side effects which limit the usage of IVIG, but studies about its benefits in many diseases for which no definite success has been obtained in treatment are being conducted. Considering the etiologies of diseases, strengthening the host's defense against internal and external agents is one of the most important therapeutic aims of medicine. IVIG which has an important role to achieve this will be continued to be used with further development in terms of safety and quality and with wider production.

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