

Market Investigation of Products Based on Plasma Derived Therapeutic Proteins

By

Nidhish Gaurav

*Dissertation submitted for the partial fulfillment of the
MBA Pharmaceutical Management*

Academic year, 2016-2018



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TO WHOMSOEVER MAY CONCERN

This is to certify that **Nidhish Gaurav** student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone internship training at **PlasmaGen Bioscience (P) Ltd.** from **5th February 2018 to 4th May 2018**.

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish him all success in all his future endeavors.



Dr. (Col) Ashok Kaushik



Dean, Academics and Student Affairs
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Dr. Saurabh Kumar Banerjee

Associate Professor
The IIHMR University, Jaipur

15th May, 2018

To whomsoever concerned

This is to certify that **Mr. Nidhish Gaurav** (Employee code – 348) working with PlasmaGen Biosciences (P) Ltd as Executive – Sales & Marketing, has successfully completed his dissertation on the topic **“Market Investigation of Products based on Plasma Derived Therapeutic Proteins”** during the period 5th February, 2018 to 4th May, 2018 under the supervision of Mr. Anant Bharne (GM – Sales & Marketing), Mr. Rakin Khan (Product Management Executive) and Ms. Payal Shobhwani (Product Executive).

For PlasmaGen Biosciences (P) Ltd.,


15/05/18
AARTHI G R
SR. MANAGER – HR & ADMIN

A circular purple stamp with the text 'M/s. PlasmaGen Biosciences Pvt. Ltd.' around the perimeter and 'BANGALORE-18' in the center.

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **Market Investigation of products based on Derived Therapeutic Proteins** and submitted by (Name) **Mr. Nidhish Gaurav**, Enrollment No.-0086, under the supervision of **Dr. Saurabh Kumar Banerjee** for award of MBA in Pharmaceutical Management of the University carried out during the period from **Febriary05,2018 to May04, 2018** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Nidhish Gaurav
Signature 17/05/2018

Acknowledgement

Without a proper combination of inspection and perspiration, it's not easy to achieve anything. There is always a sense of gratitude, which we express to others for the help and the needy services they rendered during the different phases of our lives. I have taken efforts in this project. However, it would not have been possible without the kind support and help of many individuals and organizations. I would like to extend my sincere thanks to all of them.

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ABBREVIATIONS

CDSCO	Central Drug and Standard Control Organization
DGFT	Director General of Foreign Trade
DIC	Disseminated Intravascular Coagulation
FFP	Fresh Frozen Plasma
GBS	Guillain Bare Syndrome
HSA	Human Serum Albumin
IPPC	International Plasma Protein Congress
ITP	Idiopathic Thrombocytopenia Purpura
IVIg	Intravenous Immunoglobulin
MRB	Market Research Bureau
NACO	National AIDS Control Organization
NIB	National Institute of Biologicals
PCV	Packed Cell Volume
PPTA	Plasma Protein Therapeutic Association
SCID	Severe Combined Immunodeficiency
VWF	Von Willebrand Factor
WFH	World Federation of Hemophilia

EXECUTIVE SUMMARY

plasma proteins have a wide range of therapeutic applications in various diseases for all age groups, with over one million people worldwide receiving plasma therapeutics every year, under various therapeutic purposes, viz. burn, shock & trauma, lung & liver disorders, immune deficiencies etc.

A related development has been the introduction of recombinant products as a substitute to Plasma-derived proteins, for therapeutic purposes. (For products like Factor VIII & Factor IX) Currently the branded products of Albumin, Intravenous Immunoglobulin (IVIg) and Clotting Factor VIII is available in the Indian market.

The aim of the study is to carry out the usage pattern of products based on plasma protein therapies by the Medical Fraternity in Bangalore (Karnataka) and understand the market for the plasma derived therapeutic products.

The primary analysis and secondary analysis were carried out for the project work. The study was carried out in the Bangalore(Karnataka). One hundred twenty doctors were covered in the research. The specialties covered were Gynecologists, Hemato-oncologists, Intensivists, Neuro-physicians, Pediatricians, Physicians and Surgeons. The research brought to the light the following key findings:

From Doctors

- 100% of the respondents interviewed prescribe the plasma products to their patients.
- Neuro-physicians were using the IVIg for new indications like, GBS, CIDP, CLL, Evans Syndrome, Stiff person Syndrome and Dermatomyositis.
- Pediatricians were using the plasma products in neonatal liver disease and preterm baby.
- Similarly, the General Surgeons are using the human plasma in the post-operative patients.
- 77% of the respondents were aware of the existing brands of the plasma product category.

- 23% of respondents are not satisfied with available plasma products in the market and they were looking for the benefits such as cost of the product, minimum side effects etc.

Company profile:

PlasmaGen BioSciences is an Indian Bio-pharmaceutical organization specializing exclusively in Plasma Protein Therapy .

Headquartered in Bangalore- India, PlasmaGen has been making every effort in the domain of Plasma Product Industry and has become an Imperative one stop destination for the medical fraternity for most of the plasma products need. We have a basket of plasma products and the widest range of immunoglobulins in India catering to the requisites of various realms viz. Hematology, Oncology, Immunology, Pediatrics, Rheumatology, Dermatology and Neurology

South Asian Association for Regional Co-operation (SAARC) includes 8 countries; India, Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, Pakistan and Sri Lanka, these countries not only share geographical proximity and political agenda but also share many common social concerns- Healthcare, Education, Economic Infrastructure and many more .

SAARC region share similar challenges when it comes to awareness, accessibility, availability and affordability of safe plasma products because of the limited consistent supply of safe plasma and low plasma fractionation capacity .

We therefore pursue a vision of ushering in the Plasma Protein industry in SAARC region & endeavor to provide an extensive assortment of safe plasma products to enrich the quality of life of patients. This is a step working towards addressing the very contemporary concept of regional self-sufficiency .

PlasmaGen BioSciences, having a niche and expertise in the cosmos of plasma product therapies; also works closely with the government on various plasma policies and hemovigilance, which can be extended and leveraged for growth of this industry in entire SAARC region .

PlasmaGen BioSciences was established in the year 2010 on September 7th.

PlasmaGen realizes a huge gap that exists between the availability of plasma products and the requisite of its therapies in Asia. As a matter of fact, Asia seems to hold about 60% of the world's population, but in terms of global plasma fractionation capacity it merely accounts for about 20% a huge imbalance .

India with 1.32 Billion people, accounts for almost 18% of the global population. The access to healthcare services is quite challenging, as the affordability varies to a great degree. It collects about 10 million units of blood units every year and componentizes only 40 % of it. Therefore, domestically plasma availability is very low and so is the case with fractionation capacity .

In terms of Self Sufficiency Ratio (SSR); India stands at 35-40% where consumption rates for two important plasma proteins- Albumin and IVIG, far surpass the rates of production, thereby making establishment of a plasma products company not just a scientific necessity but also an Indispensable socio-economic obligation .



Also On



PlasmaGen BioSciences Pvt. Ltd.

Is an Indian Biopharmaceutical company specializing in Plasma Protein Therapy. We pursue a vision of ushering in the Plasma Protein industry in India & SAARC nations. PGB aims to provide a wide range of safe plasma products to improve the health & quality of life of patients.

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Introduction

Plasma products have shown a tremendous growth over the past year. Although discovery of recombinant product has challenged naturally derived plasma protein preparations but still in developing countries like India, plasma products are gaining popularity due to their higher acceptability by elder population. Reasons for growth of plasma products are due to uses in new indications, higher purification process, growing concern among Indian Biopharmaceutical industry like **PlasmaGenBiosciences**, Reliance, Intasetc .

Hence lots of biopharmaceutical companies are entering into this segment and for effective launching of their products and gaining the maximum market share, marketers are trying to identify the prescribing habits and pattern of doctors. Lots of market research organization has provided useful data related to this segment .

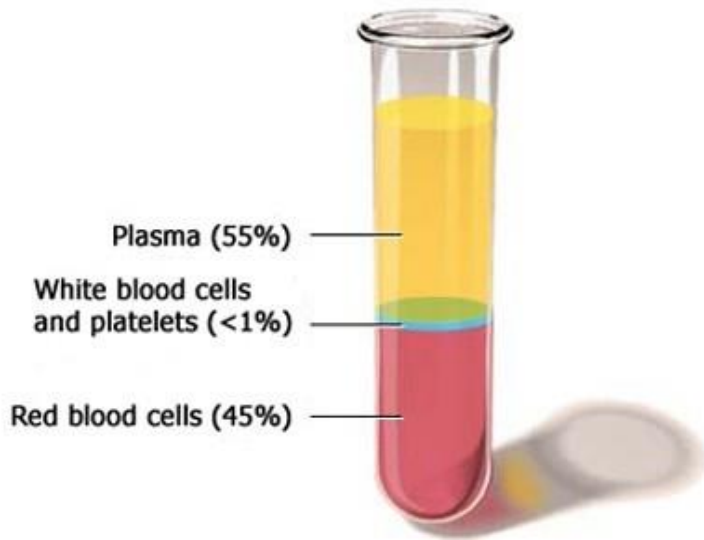
BLOOD/ PLASMA

Two ways of saving life:

Whole blood consists of two main components; red blood cells which represent about 45% of the volume of a unit of blood, and plasma, which is the liquid portion of blood, making up the remaining 55%. Whole blood collected from a donor can be separated into these two components by centrifugation .

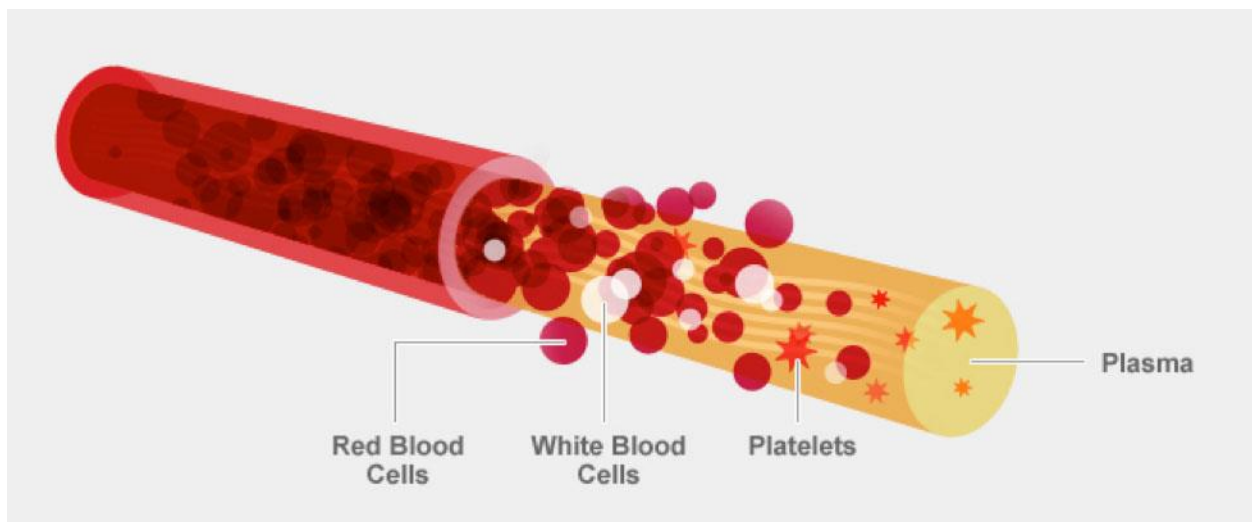
Plasma can be directly collected from a person by a procedure called “plasmapheresis” in which whole blood is drawn from a donor’s vein into a machine which separates plasma from the red cells by filtration or centrifugation .

Once the red cells are separated from the plasma, they are returned to the donor using the same vein or a different one, depending on the machine used. The human body regenerates plasma within a few days, unlike red blood cells, which need a few weeks. For this reason, a donor can donate plasma more frequently – up to twice a week in the United States – than whole blood .



Red cells and whole blood are used to treat traumatic or surgical blood loss, as well as anemia. Plasma is used in several indications, deficiencies of certain coagulation factors, as well as trauma, shock and many other medical conditions. Plasma serves also as the raw material to manufacture several “plasma-derived” drugs through an industrial process called “fractionation” which isolates each “fraction” of the plasma by means of various chemical and physical methods and turns them into life-saving drugs: coagulation factor concentrates, immunoglobulins, albumin and others .

Blood Components:



Erythrocytes (Red Blood Cells)

Red blood cells (RBCs), also called erythrocytes, are the most common type of blood cell and the vertebrate's principal means of delivering oxygen (O_2) to the body tissues—via blood flow through the circulatory system. RBCs take up oxygen in the lungs, or gills of fish, and release it into tissues while squeezing through the body's capillaries.

The cytoplasm of erythrocytes is rich in hemoglobin, an iron-containing biomolecule that can bind oxygen and is responsible for the red color of the cells. The cell membrane is composed of proteins and lipids and this structure provides properties essential for physiological cell function such as deformability and stability while traversing the circulatory system and specifically the capillary network.

In humans, mature red blood cells are flexible and oval biconcave disks. They lack a cell nucleus and most organelles, in order to accommodate maximum space for hemoglobin; they can be viewed as sacks of hemoglobin, with a plasma membrane as the sack. Approximately 2.4 million new erythrocytes are produced per second in human adults. The cells develop in the bone marrow and circulate for about 100–120 days in the body before their components are recycled by macrophages. Each circulation takes about 60 seconds (one minute). Approximately a quarter of the cells in the human body are red blood cells. Nearly half of the blood's volume (40% to 45%) is red blood cells .

Leukocytes (White Blood Cells)

White blood cells (WBCs), also called leukocytes or leucocytes, are the cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders. All white blood cells are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem cells. Leukocytes are found throughout the body, including the blood and lymphatic system .

All white blood cells have nuclei, which distinguishes them from the other blood cells, the anucleate red blood cells (RBCs) and platelets. Types of white blood cells can be classified in standard ways. Two pairs of broadest categories classify them either by structure (granulocytes or agranulocytes) or by cell division lineage (myeloid cells or lymphoid cells). These broadest categories can be further divided into the five main types: neutrophils, eosinophils (acidophils), basophils, lymphocytes, and monocytes. These

types are distinguished by their physical and functional characteristics. Monocytes and neutrophils are phagocytic. Further subtypes can be classified; for example, among lymphocytes, there are B cells, T cells, and NK cells .

The number of leukocytes in the blood is often an indicator of disease, and thus the WBC count is an important subset of the complete blood count. The normal white cell count is usually between $4 \times 10^9/L$ and $11 \times 10^9/L$. In the US this is usually expressed as 4,000 to 11,000 white blood cells per microliter of blood. They make up approximately 1% of the total blood volume in a healthy adult, making them substantially less numerous than the RBCs at 40% to 45%. However, this 1% of the blood makes a large difference to health, because immunity depends on it. An increase in the number of leukocytes over the upper limits is called leukocytosis. It is normal when it is part of healthy immune responses, which happen frequently. It is occasionally abnormal, when it is neoplastic or autoimmune in origin. A decrease below the lower limit is called leukopenia. This indicates a weakened immune system .

Thrombocytes (Platelets)

Platelets, also called thrombocytes (thrombo + -cytes, "blood clot cell"), are a component of blood whose function (along with the coagulation factors) is to stop bleeding by clumping and clotting blood vessel injuries. Platelets have no cell nucleus: they are fragments of cytoplasm that are derived from the megakaryocytes of the bone marrow, and then enter the circulation. These inactivated platelets are biconvex discoid (lens-shaped) structures, 2–3 μm in greatest diameter. Platelets are found only in mammals, whereas in other animals (e.g. birds, amphibians) thrombocytes circulate as intact mononuclear cells .

On a stained blood smear, platelets appear as dark purple spots, about 20% the diameter of red blood cells. The smear is used to examine platelets for size, shape, qualitative number, and clumping. The ratio of platelets to red blood cells in a healthy adult range from 1:10 to 1:20 .

The main function of platelets is to contribute to hemostasis: the process of stopping bleeding at the site of interrupted endothelium. They gather at the site and unless the interruption is physically too large, they plug the hole. First, platelets attach to substances outside the interrupted endothelium: *adhesion*. Second, they change shape, turn on receptors and secrete chemical messengers: *activation*. Third, they connect to each other through receptor bridges: *aggregation*. Formation of this platelet plug (primary hemostasis) is associated with

activation of the coagulation cascade with resultant fibrin deposition and linking (secondary hemostasis). These processes may overlap: the spectrum is from a predominantly platelet plug, or "white clot" to a predominantly fibrin clot, or "red clot" or the more typical mixture. The result is the *clot*. Some would add the subsequent clot retraction and platelet inhibition as fourth and fifth steps to the completion of the process and still others a sixth step wound repair.

Plasma

Blood plasma is a yellowish colored liquid component of blood that normally holds the blood cells in whole blood in suspension; this makes plasma the extracellular matrix of blood cells. It makes up about 55% of the body's total blood volume. It is the intravascular fluid of extracellular fluid (all body fluid outside cells). It is mostly water (up to 95% by volume), and contains dissolved proteins (6–8%) (i.e.—serum albumins, globulins, and fibrinogen), glucose, clotting factors, electrolytes (Na^+ , Ca^{2+} , Mg^{2+} , HCO_3^- , Cl^- , etc.), hormones, carbon dioxide (plasma being the main medium for excretory product transportation) and oxygen. Plasma also serves as the protein reserve of the human body. It plays a vital role in an intravascular osmotic effect that keeps electrolytes in balanced form and protects the body from infection and other blood disorders .

Blood plasma is separated from the blood by spinning a tube of fresh blood containing an anticoagulant in a centrifuge until the blood cells fall to the bottom of the tube. The blood plasma is then poured or drawn off. Blood plasma has a density of approximately 1025 kg/m^3 , or 1.025 g/ml .

Plasma Products

Plasma products are made by dividing the plasma into different proteins and other substances. Each plasma products have different medical uses. They serve many different functions, including

- Circulatory transport molecules for lipids, hormones and vitamins
- Enzymes, complement components, protease inhibitors and kinin precursors.
- Regulation of acellular activity and functioning and in the immune system.
- Protein reserve for the body.
- Maintenance of blood pH

Types of Plasma Products:

1. **Whole Plasma:** is only used when someone is bleeding and has lost a lot of blood, for example after childbirth or during cardiac surgery. It helps the blood to clot and decrease bleeding .
2. **Globulin**(Immunoglobulin)
3. **Specialized Immunoglobulin products:**are used to help produce stronger antibodies against disease like tetanus, hepatitis, chicken-pox, and rabies. Ex. Hepatitis-B immunoglobulin, Tetanus immunoglobulin, Anti rhesus immunoglobulin .
4. **Albumin:** contained in plasma is extremely beneficial for burn victims.
5. **Clotting factors:**
 - **Factor VIII** is used in the treatment of type A hemophilia, the most common type. Hemophilia is when blood does not clot properly, and this type of hemophilia is caused by a lack of factor VIII.
 - **Factor IX** is used for treating sufferers of Christmas disease, which is a rarer and more serious form of hemophilia (type B).
6. Other plasma derivatives include wound-healing products and humanalpha-1 antitrypsin which is used in the pulmonary disease therapy.

Therapeutic Products Obtained from Plasma

Albumin	Von Willebrand factor
Immunoglobulin	Fibrinogen
Factor VIII	Fibrin sealant
Factor IX	Prothrombin complex
Factor VII	Act. Prothrombin complex
Factor VIIa	Antithrombin
Factor XI	Alpha-1- Antitrypsin

Table 1:Therapeutic product obtained from plasma

Market information of plasma products in India

There is a gap in the demand and supply of the plasma products and the products are not available on the regular Basis. The market of these products is estimated to about 500 crores annually.

Products specifications and applications:

Products	Indications	Patients in India
Albumin	• Volume Replacement • Formulation Excipients • Presentation Vehicle	Millions of individuals (acute cases)
Intravenous Immunoglobulins (IVIG)	1. Primary immunodeficiency 2. Kawasaki disease 3. Immune thrombocytopenic purpura 4. GBS 5. CIDP	Roughly half chronic, half acute (new indications will expand patients populations)
Hyper-immune Immunoglobulins	RH(D) Tetanus Hepatitis-B	
Factor VIII	Hemophilia-A	1 lac patients
Factor IX	Hemophilia-B	40,000 patients

Table 2: Specification and application of therapeutic products

Intravenous Immunoglobulins (IVIG)

Primary Immunodeficiency: -

Immunoglobulin replacement therapy via the IV or SC route is required in patients with certain PI diseases characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infection.

Replacement therapy for agammaglobulinemia and hypogammaglobulinemia in well-described immunodeficiencies such as X-linked agammaglobulinemia (XLA) or common variable immunodeficiency (CVID) is necessary and life-saving. Other more genetically complex PIs, however, may also involve defects in antibody function that contribute to an increased susceptibility to infections. Over 250 distinct PIs have been described to date, and with the advent of whole-exome sequencing, new PIs continue to be discovered at a rapid pace. The effects of these newly described gene defects on the humoral immune system may not be fully understood or qualified with currently commercially available tests of antibody level and function. Therefore, the indications for immunoglobulin therapy in various clinical presentations of immunodeficiency are likely to broaden as the disorders are better understood, considering that most of PI diseases involve antibody deficiency. A recent publication reviewed the controversies surrounding immunoglobulin therapy, including the need for better laboratory assays of functional antibody responses and better clinical and microbiological evaluation and characterization of the recurrent infections seen in antibody-deficient patients.

10 warning signs of PID:

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effects.
4. Two or more pneumonias within 1 year
5. Failure of an infant to gain weight or grow normally.
7. Recurrent, deep skin or organ abscesses.
8. Persistent thrush in mouth or fungal infection on skin.

9. Need for intravenous antibiotics to clear infections.
10. Two or more deep seated infections including septicemia.

IVIG Dosage: single dose of 0.4-0.6gm /Kg every 3-4 weeks

Kawasaki Disease

Kawasaki disease is the most common form of vasculitis in children and if left untreated a quarter will develop serious coronary artery aneurysms. The first successful report of using IVIG for Kawasaki disease in 14 patients came in 1983 and since then meta-analyses have confirmed that high-dose IVIG is highly efficacious in reducing coronary artery aneurysms when combined with aspirin. More recently, a Cochrane review analyzed 59 trials and found that a single high dose of IVIG (2g/kg) led to a reduction in coronary artery aneurysms at 30 days. It is therefore of high priority for Kawasaki patients to be treated with IVIG and aspirin within 10 days of onset.

❖ Acute Stage

- Conjunctivitis (Nonexudative bilateral)
- Rashes
- Adenopathy of lymph
- Strawberry tongue
- Hands, feet & perianal erythema
- Burn (Fever 1-2 weeks)

❖ Subacute Stage

- Fever up to 3-4 weeks
- Thrombocytosis
- Desquamation of the digits
- Coronary Aneurysms
- Anorexia
- Conjunctival injection

❖ Convalescent Stage

- Myocardial infarction
- Large aneurysms & detection of new aneurysms
- Extremity Changes

- Deep transverse grooves across the nails

❖ **Chronic Stage**

- Developed cardiac complications
- Aneurysm formed in childhood may rupture in adulthood

IVIG Dosage: single dose of 2gm /Kg of body weight

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is a disorder that may affect patients of all ages. Pharmacologic treatment of all children with ITP may not be required because most children will spontaneously recover. Treatment is usually provided to those children at greatest risk for bleeding complications and those with chronic refractory disease. Commonly used therapeutic modalities include systemic corticosteroids, anti-D, IVIG, plasmapheresis, rituximab, and combinations of these. The effectiveness of IVIG in increasing platelet counts has been supported in numerous studies, resulting in an FDA-approved indication of its use. Importantly, high-dose IVIG has been compared to systemic corticosteroids in randomized, multicenter trials, and was found to provide a clinically relevant advantage. Thus, at present, IVIG remains an important and useful treatment modality for preventing or controlling bleeding in the more severe presentations of immune-mediated thrombocytopenia. Anti-Rh(D) products have also been used as first-line therapy in patients with primary ITP. However, this product should be avoided in patients with preexisting hemolysis and other risk factors because the administration of anti-Rh(D) has been rarely associated with severe intravascular hemolysis, disseminated intravascular coagulation, and acute renal failure. Corticosteroids, IVIG, or anti-D immunoglobulin are considered first-line therapies for ITP.

IVIG Dosage: single dose of 0.8-1gm /Kg of body weight (children)

IVIG Dosage: single dose of 1gm /Kg of body weight (Adult)

Guillain-Barré syndrome

GBS is a polyradiculopathy characterized by acute progressive motor weakness of the extremities, bulbar and facial musculature, and sometimes sensory or autonomic dysfunction. It is thought to result from immunologic destruction of myelin or Schwann cells within the peripheral nervous system. Therefore, it is commonly treated with corticosteroids, PE, and IVIG. Data from the first large-scale, randomized, open-label, controlled trial of IVIG (0.4g/kg/day for 5 days) versus PE suggested that the clinical outcomes were at least comparable. A multicenter, randomized, blinded, controlled trial involving 383 patients from Europe, Australia, and North America revealed no significant differences in mean disability grade between patients treated with PE, IVIG, or PE followed by IVIG. The addition of methylprednisolone (0.5g/day for 5 days) after a course of IVIG did not show a significant benefit in a multicenter, randomized, double-blind, placebo-controlled study in 233 patients. Several other studies that have compared IVIG to supportive measures or PE in children and adults showed similar findings, but patients were not always randomized, and investigators were not blinded to the treatments. A systematic review of data from randomized trials revealed no significant differences in any of the outcome measures between IVIG and PE. None of the treatments significantly reduced mortality. Several Cochrane reviews have provided moderate-quality evidence that, in severe disease, IVIG started within 2 weeks from onset hastens recovery as much as does PE.

IVIG Dosage: single dose of 0.4gm /Kg/day for 5 days

Chronic inflammatory demyelinating polyneuropathy

CIDP is characterized by progressive symmetric weakness, sensory loss, and areflexia. Contrary to the acute nature of GBS, signs of progression occur over months, with immunologic damage targeting the myelin sheaths of peripheral nerves. It has been historically treated with corticosteroids, PE, or, in more resistant cases, cytotoxic immunosuppressive drugs. Earlier RCTs showed that IVIG improved disability within 2-6 weeks compared with placebo, and had efficacy similar to that of PE and prednisolone, although with an increased quality of life. The standard dose is 0.4 g/kg/day for 5 days, but in relapsing patients this dose may need to be repeated every 2-8 weeks to maintain improvement.

IVIG Dosage: single dose of 0.4gm /Kg/day for 5 days

Multifocal motor neuropathy

Several randomized, double-blind, placebo-controlled, crossover clinical trials have shown IVIG to provide efficacy in treating MMN, a chronic inflammatory condition that selectively affects the motor nerves (especially the radial, ulnar, median, and common peroneal). IVIG is now FDA-approved for use in treating MMN. Using a dose of 0.4-0.5g/kg/day for 5 consecutive days, >80% of patients reported improvement as assessed by self-evaluation scores. IVIG had no consistent effect on IgM anti-ganglioside M1 antibody titers, nor was it invariably accompanied by improvement in motor conduction block or Medical Research Council scores.

IVIG Dosage: single dose of 0.4gm /Kg/day for 5 days

Myasthenia gravis:

The benefit in MG of IVIG (0.4 g/kg/ day for 3-5 days) was comparable to that of PE in 2 randomized, comparative studies, with a decrease acetylcholine receptor antibody concentration in one study and the quantified MG clinical score in the other. In the older study, patient tolerance of IVIG was generally better than that of PE. However, Class I evidence that IVIG and PE have comparable efficacy and are similarly tolerated in adult patients with moderate to severe MG within 2 weeks of treatment was recently reported, and the only factor predicting response to treatment was baseline disease severity. Nonetheless, a randomized, placebo-controlled study failed to demonstrate a significant effect after 6 weeks of IVIG therapy. IVIG was considered of possible benefit in myasthenic crises and juvenile myasthenia, and in preparing myasthenic patients for surgery.

IVIG Dosage: single dose of 0.4gm /Kg/day for 5 days

INDIA Market Overview:

India is the seventh largest country in terms of area and the second most populous country in the world. It has a plethora of natural resources and assets like the rich agricultural lands, deep gold and gemstone mines, some of the largest rivers, and, most importantly, its 1.2 billion people, which hold huge potential in more ways than one¹ .

Plasma is one such resource, which India could have in abundance, but its potential is still unrealized. Being the youngest and second most populous country, India has a huge blood/plasma donor base which can greatly contribute to the local, as well as, global plasma product industry .

Unfortunately for a variety of reasons, this potential is not explored and tapped to its fullest. The challenges in the Indian plasma industry are intense and prevalent at all the stages right from the start until the end. India collects about 10 million of blood at more than 2700 blood banks across the country .

These blood banks are in public, private, charitable, and hospital settings. As per the Drug and Cosmetic Act, each unit of blood is tested for HIV-I and HIV-II antibodies, Malaria, Syphilis, Hepatitis B surface antigen and Hepatitis C virus antibody and componentized within 6 hours of collection

Indian Scenario

India needs about 900,000 liters of plasma proteins per year. The overall demand of various plasma derived products is depicted in the table 3 Import of size of these products in year 2014-15 and their cost .

Table 3: overall current demand of albumin, coagulation factor VIII and IX, and intravenous immunoglobulin			
Albumin	IVIG	Factor VIII	Factor IX

8-10 lac vials	3 -4 lac vials	80-100 million IUs	10-15 Million IUs
20 gm/ 100 ml	5 gm/100 ml	250 IUs	500 IUs

Table 3:Current Demand of IVIG

Size of indigenously manufactured these products in year 2014-15.			
1	albumin:	: 3 lac vials	With NPPA rate: Rs. 4038 per vial: Rs. 120 Cr.
2	IVIG	60000 vials	at the rate: Rs. 7500/vial: Rs. 45 Cr
3	Factor VIII	It is largely imported at the rate of Rs. 13-22 IUs	

Table 4:No. of Vials Manufactured

The Indian market for intravenous immunoglobulin (IVIG) products and therapies is heading in a positive direction due to several innovative techniques and advantages it offers to clinicians worldwide .

The rising patient pool suffering from immunological and neurological disorders, mounting geriatric population, and rising production of IVIG products are also expected to have a significant positive impact on market's future growth prospects .

The Indian intravenous immunoglobulin (IVIG) market is largely consolidated, with top four players:

1. Reliance Life Sciences
2. Intas Pharmaceuticals Ltd.
3. PlasmaGen BioSciences
4. Wockhardt Limited

Company Landscape of IVIg:

Company	Brand name	Strength	MRP	Market share in unit(Per Month)	Market share in Crore
Reliance	Immunorel	5%,	₹14697	5250	7.71
Intas	Globucel	5%, 10%	₹14697	3245	4.79
PlasmaGen	PlasmaGlob	5%,	₹14697	1700	2.49
Wockhardt	Globuwok	5%,	₹14697	1365	2.00
Bharat Serum	Gamma IV	5%,	₹14697	720	1.05
Biocon	Ivnex	5%,	₹14697	345	0.50
Emcure	Emglobulin	5%	₹14697	90	.013
GSK	Seroglobulin	5%	₹14697	150	0.22
India buls	Immuglo	5%	₹14697	225	.33

Table 5:IVIIG product available in India

Market coverage

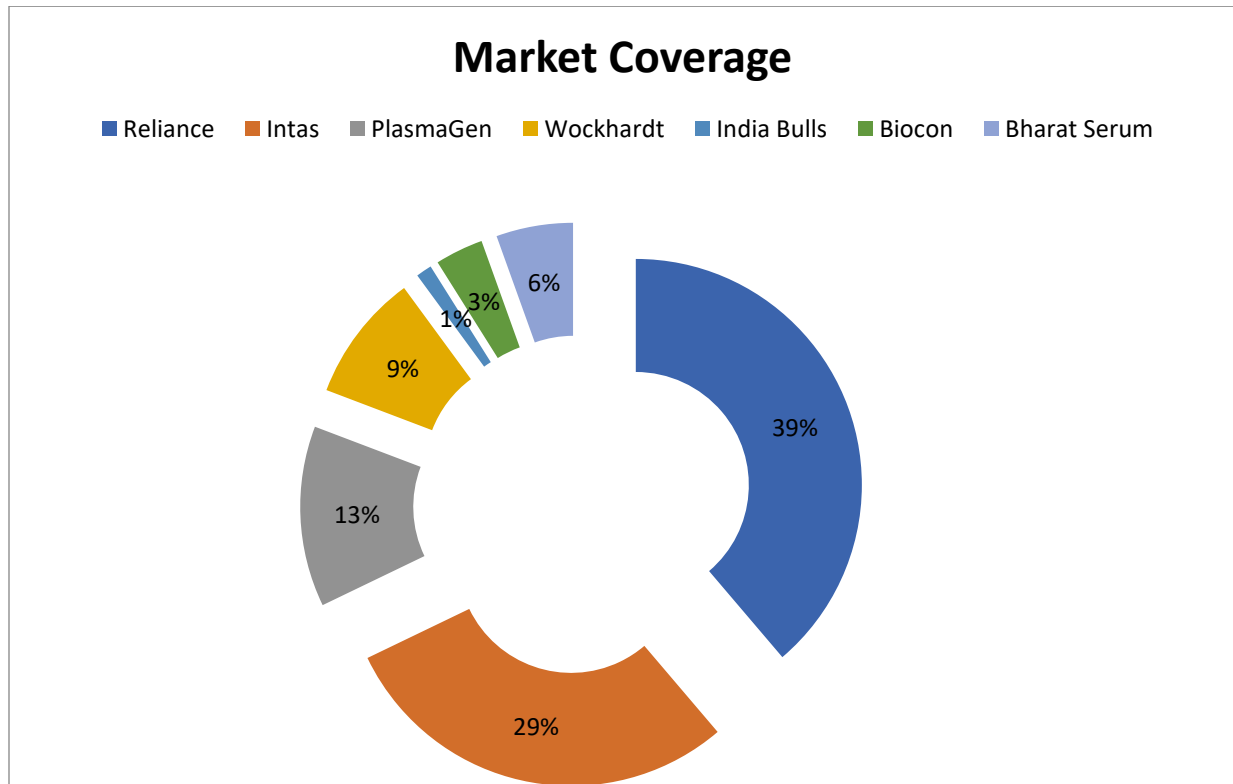


Figure 1: Monthly Market coverage of Indian companies in India

LITERATURE REVIEW

Plasma proteins have a wide range of therapeutic applications in various diseases for all age of groups, with over one million people worldwide receiving plasma therapeutic every year, under various therapeutic purposes, viz. burn, shock & trauma, lung and liver disorders, immune deficiencies etc. As many of these therapies are repetitive and have no substitute, the regular availability of plasma therapeutics is essential .

The relatively high cost is associated with availability of good quality plasma coupled with relatively high fractionation charges because of the state of the art fractionation technologies and quality assurance standards involved, ensures that there exists a high level of correlation between purchasing power parity (and consequently per capita healthcare expenditure) and demand for high end therapeutic product like plasma derived proteins .

A related development has been the introduction of recombinant product as a substitute to plasma- derived proteins, for therapeutics purposes (for products like Factor VIII & Factor IX) recombinant products meet higher safety standards as compared to plasma derived proteins (the former having been cloned synthetically, as against the latter having been sterilized using virus inactivation methods). However, recombinant technology makes these products much more expansive than plasma derived products. Also, long term usage of recombinant products has been found to cause certain immunological effects which is proving to be very discouraging of the future for recombinant substitute for plasma proteins .

According to a study conducted by Market research bureau- only developed countries are gradually moving toward usage of recombinant products but the market for plasma-derived proteins is growing continuously in the developing countries like India .

In its 2016 report, blood products and blood testing markets, Kalorama indicates that the strong promotion of blood donations on behalf of collection agencies, along with synthetic blood products, is scarcely meeting the demand for this industry's products and this continued need is driving up blood prices. Stored and distributed blood, originally developed to treat war casualties, is now used primarily for testing and transfusions. Kalorama finds more than 50% of transfusions occur in patients over the age of 65, and thus attributes the growth of the blood products market to an aging population, which is inherently driving up prices .

The report titled “Blood Banking & Blood Products: A Global Strategic Business Report” revealed that the global market for Blood Banking & Blood Products is forecast to reach US\$1236million by the year 2022. Aging population, emergence of new infections and efforts to make available qualitative blood the world over are fueling market growth. Stringent regulatory and healthcare policies adopted across the world are also influencing the market for blood banking and blood products. Increasing population in developing countries such as India and China, puts pressure on demand for blood on the blood bank segment. Governments of these countries are focused on enhancing health care delivery, which includes the blood bank segments. Resultantly Asia-Pacific is projected to emerge as the fastest growing regional market over the analysis period (2015-2022) .

According to John M. Curling (consultant)- The Indian market is only 0.25% of the global plasma products market. Plasma fractionations in India face a major challenge with low price imports .

As per PRLog (Press Release)- The global plasma products market has more than doubled over the period 2015-22 because of increase in demand and prices of plasma products. The worldwide plasma supply has increased but not at the same pace as the demand for the plasma products. The global plasma products market has been segmented based on plasma proteins like immunoglobulin, albumin, clotting factors and other proteins. The IVIG or Immunoglobulin market is the largest segment of the plasma products market having more than fifty percent share of the market. The IVIG and Albumin segment has been real drivers of the global plasma products market as they witnessed double-digit growth rate over the last few years .

According to Global Blood Plasma Market Report: 2011 Edition-Recent scientific studies are leading to the discovery of new proteins in the blood plasma and their uses to treat hitherto unresolved medical conditions. The market for blood plasma products has shown continuous growth in the past years growing at a CAGR of around 10% during 2001-10 and is projected to expand steadily in the years to come .

The use of blood plasma products in developed countries is well established; however, their demand in emerging countries, such as China and India is persistently on the rise. With scientific, technological advances in medical research in developed and developing countries, there is now much room for increased usage of IVIG. New indications are being explored

whereby various blood plasma products are being put to new uses for treatment of old and new diseases. Besides this bleeding disorders and related diseases are growing requiring increased usage of blood plasma products. Ageing population is on the constant rise worldwide and the aged people are prone to develop diseases requiring more demand of blood derivatives. Furthermore, the economic growth is also responsible for higher utilization of blood plasma derivatives. Also, new proteins are being discovered in blood plasma, which are being put to new uses for treatment of various diseases .

When the first plasma-derived clotting factor concentrates were introduced in the late 1960s and 1970s, they revolutionized the treatment of bleeding disorders. People with hemophilia could not only look forward to a much longer lifespan, but for the first time they were free to travel, work and go about their everyday lives without the gnawing fear of uncontrolled bleeds .

Although early plasma-derived products were effective, they were also defective. As many people discovered in the 1970s, 1980s and 1990s, those products could transmit viruses such as hepatitis B, HIV and hepatitis C. Pharmaceutical companies responded by submitting their plasma products to a rigorous purification process, which dramatically reduced the risk of pathogen transmission. Still, when genetically engineered (recombinant) factor products first became available in the 1990s, they were not just another treatment option for people with bleeding disorders, but a safer alternative that helped prevent viral transmission .

Although many people switched to recombinant products when they became available, plasma-derived products continue to play an important role today. "The main reason is that some people—generally older individuals who grew up using plasma-derived products—feel that they work better for them," says Marion Koerper, MD, professor of pediatrics, University of California, San Francisco Medical Center .

With rigorous tests, quality checks and viral inactivation processes now in place, the risk of transmitting viruses such as HIV and hepatitis has been virtually eliminated. "The risk is extremely low at this time for known pathogens because of all the steps that the manufacturers are taking between testing the donors and testing donations, and then all the viral inactivation steps that are being applied," says Koerper .

Objectives

1. **To study the usage pattern of products based on plasma protein therapies by the Medical Fraternity in Bangalore (Karnataka).**

Scope of study:

- Doctor's awareness about the currently used plasma products.
- Effect of the attributes such as availability, free from risk of infection, cost, quality etc. on the prescription pattern.
- To examine the level of satisfaction among doctors for currently available plasma products.

2. **To study the Global growth pattern of the products based on plasma derived therapeutic proteins.**

Scope of study:

- To understand growth of the product based on plasma derived therapeutic proteins & its indications.
- To study the current scenario of product based on plasma derived therapeutic proteins & its future markets.

Research Methodology

Study Design: Descriptive study

Sampling: Non-probability, convenience sampling

Target respondents: from various govt. and private hospitals, Hematologist, Pediatrician, Intensivist, Gynecologists, Neuro-physicians

Sample Size: Number of doctors: 120

Sample area: Bangalore (Karnataka)

Tool: Questionnaire to collect primary data, Microsoft Excel for analysis

Data Collection: Primary- Through questionnaire and meeting with respondents

Study duration: 3 Month

Data Collection Tool: Primarily, Secondary Data collected (Company Annual Reports, various research articles and publications). Data was triangulated using both primary and secondary approach.

DATA ANALYSES:

1. Average number of patients examined by you in your daily practice

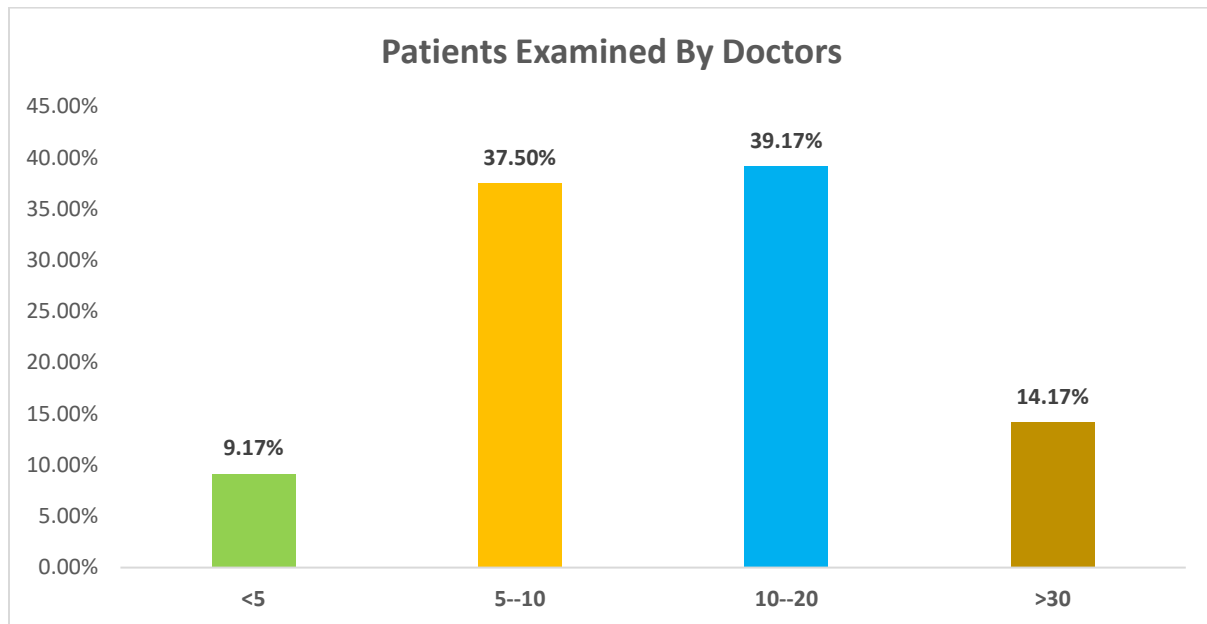


Figure 2: Patients Examined by Doctors

It was observed that in case of government hospitals the number of patients seen were in between 35-40 patients daily, where as in the case of the private hospitals the number of patients seen were in between 5-10 patients daily followed by 15-20 per day .

If there are so many patients we have a great opportunity further for many products.

2. Doctor's covered with different specialty:

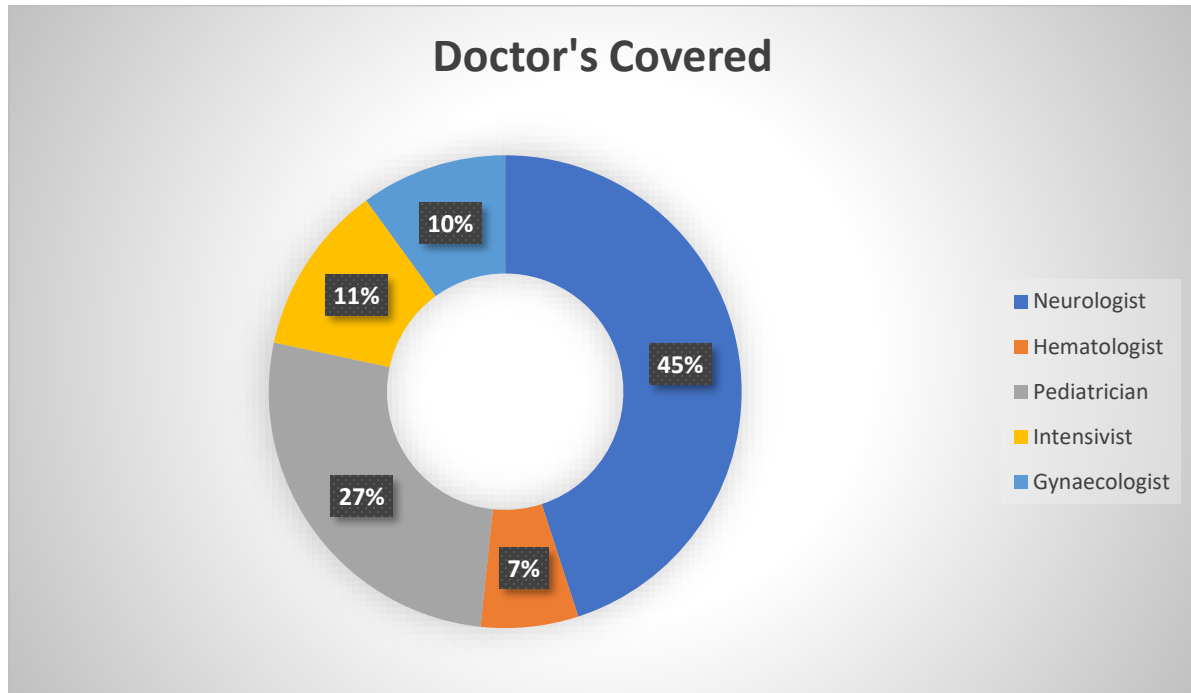
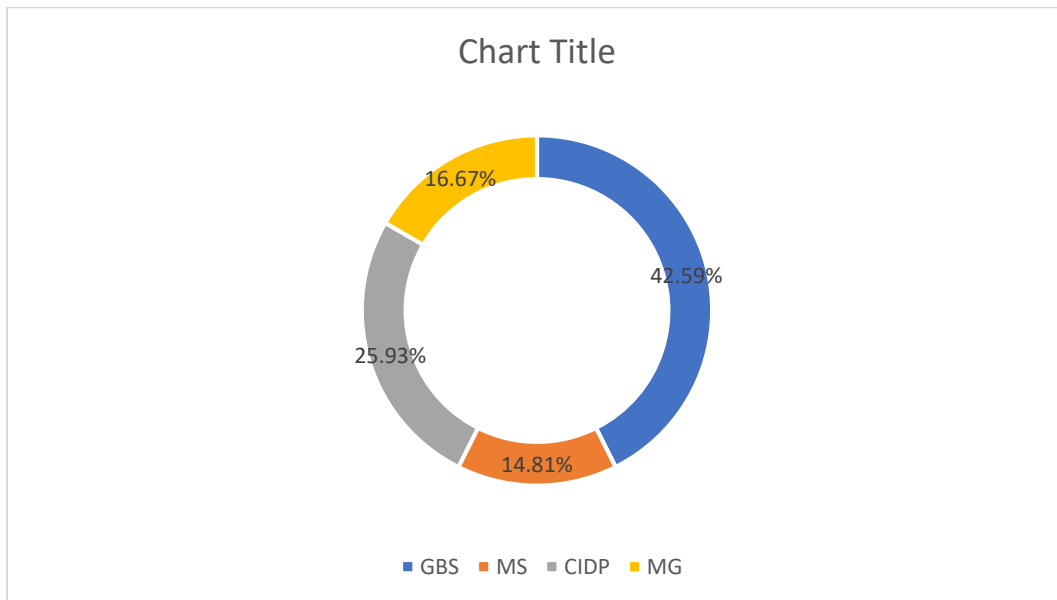


Figure 3: Total Doctor's covered

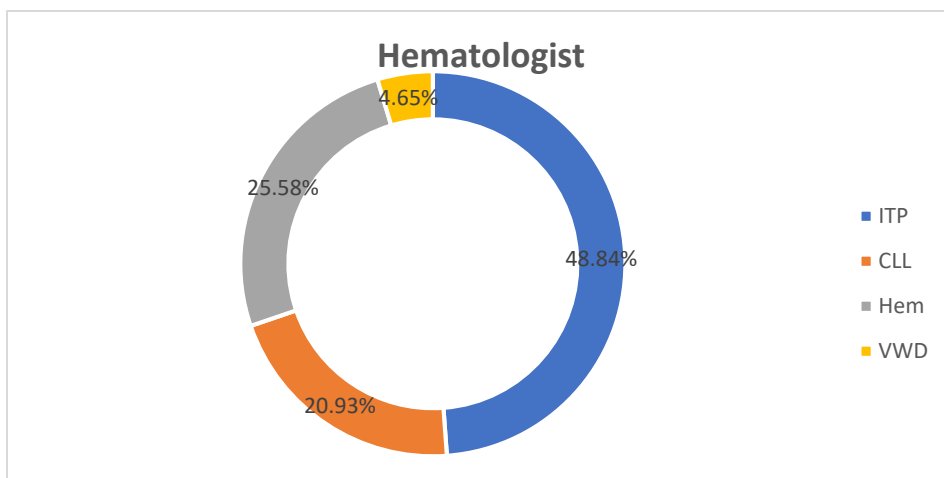
The objective of this question is to find out the percentage of patients treated by the doctor of specialty for various disease to estimate the incidence of the disease in which the plasma derived therapeutic products are prescribed. I have collected data from Bangalore region in which neurologist (45%), Hematologist (7%), Pediatrician (27%), Intensivist (11%), gynecologist (10%) covered during survey .

2.1 Percentage of patients treated for the following disease by specialty:

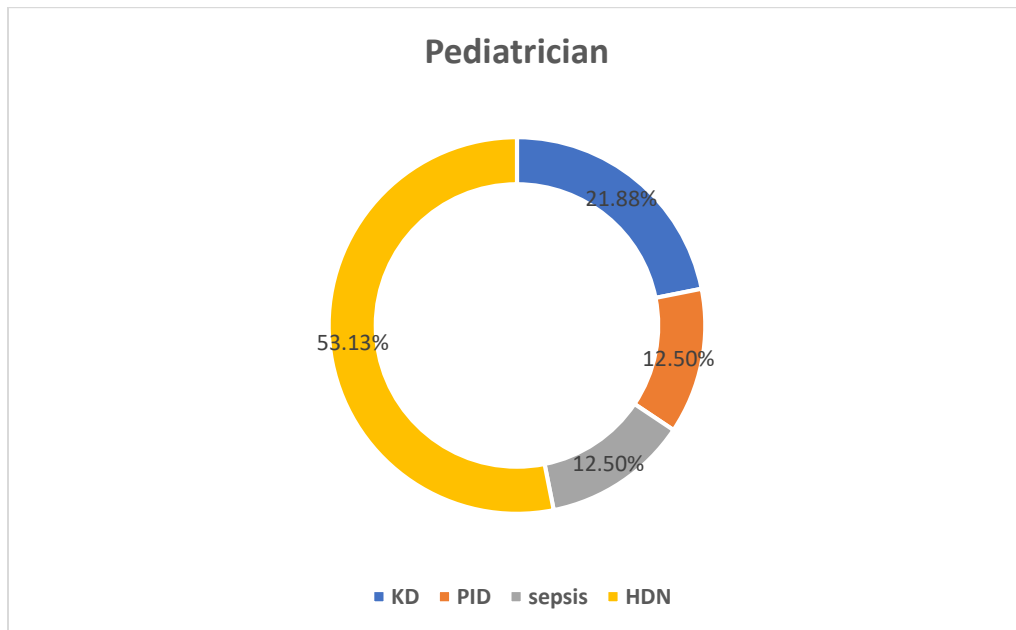


During the survey,neurologist usage IVIG in diseases like GBS (43%),MS (15%), CIDP (26%), MG (17%). GBS cases are high during summer season and in monsoon, this information I found from doctors. Disease burden is also high of GBS .

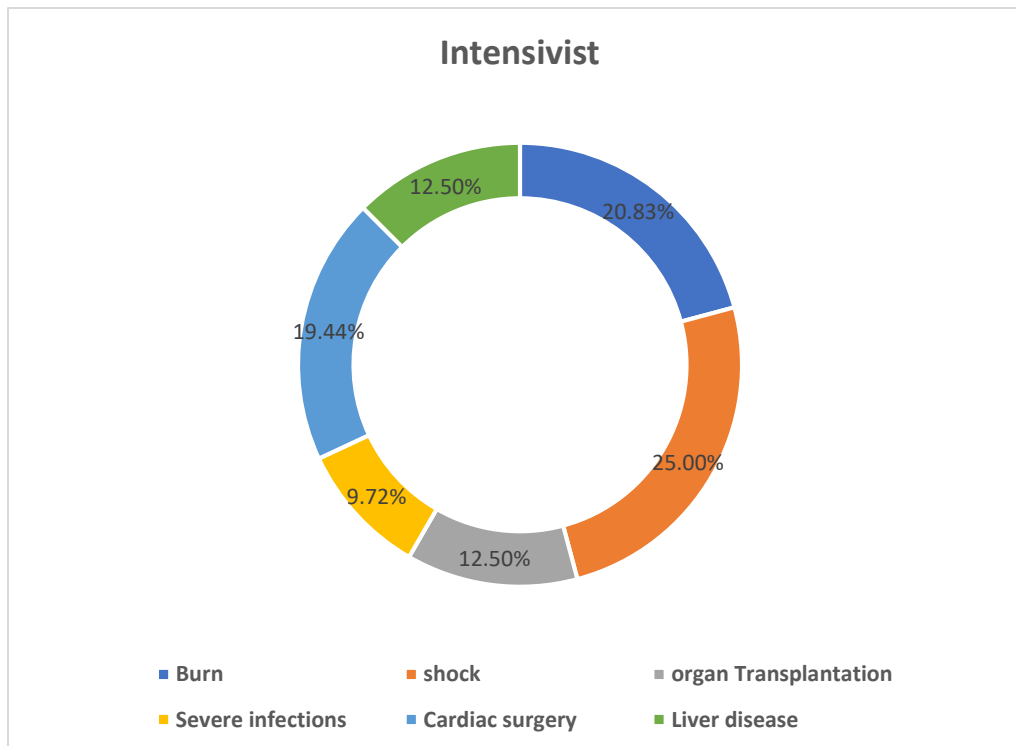
2.2 Hematologist:



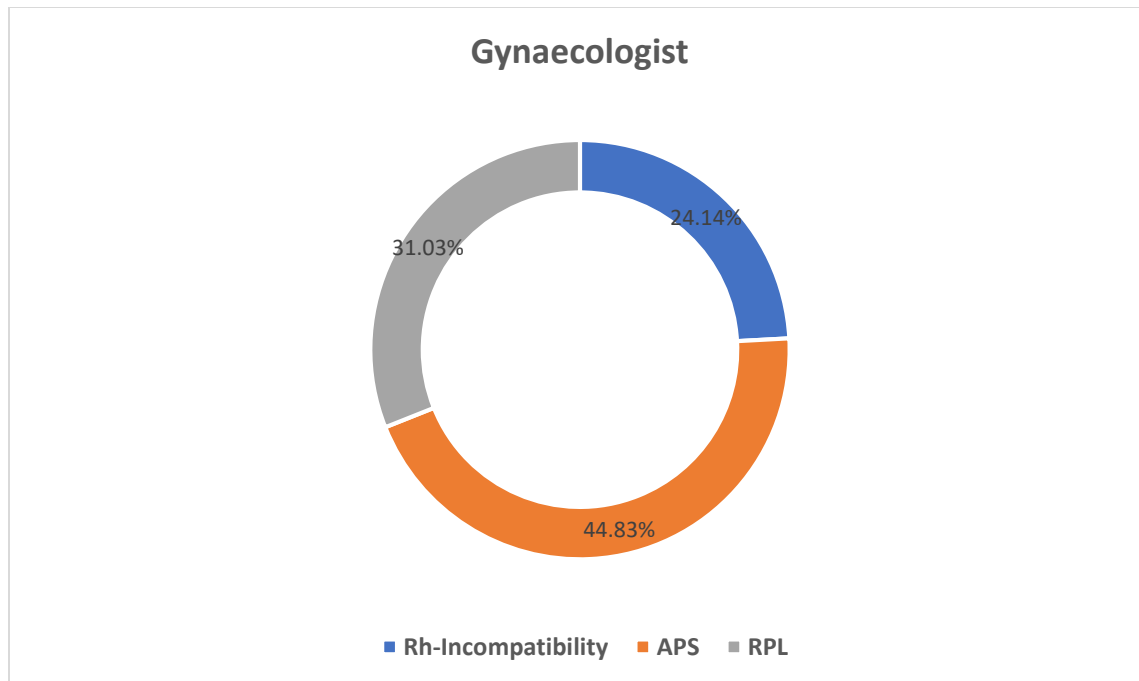
2.3 Pediatrician:



2.4 Intensivist:



2.5 Gynecologist:



In this study, I found the exact data regarding the diseases burden and examined by medical fraternity and use of plasma products in different indications of different diseases. I have collected data from neurology, hematologist, gynecologist, pediatrician and intensivist .

As I found during study some rare cases of diseases and in the off-label indications also in which plasma products are using specially IVIG. In my study mostly, plasma products used by neurologists .

3. Percentage of Doctors aware about the existing brand of plasma product in the market:

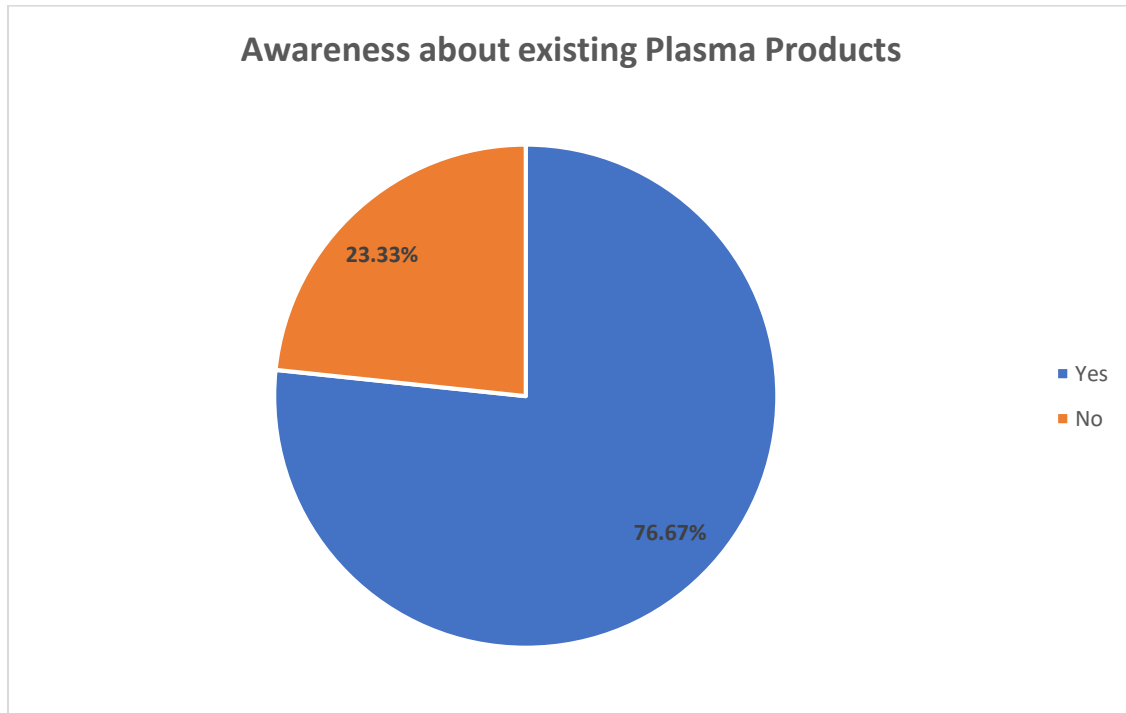


Figure 4: Awareness about existing plasma products

During conversation I asked from respondents about the existing brand of plasma products in the market and the answers which i get approx.77% doctors know about it whereas23% of them don't know .

If any doctor have idea about the plasma products segment, then it became easy for further queries and demand .

4. Percentage of Doctors having preference for a well-established brand in plasma product category:

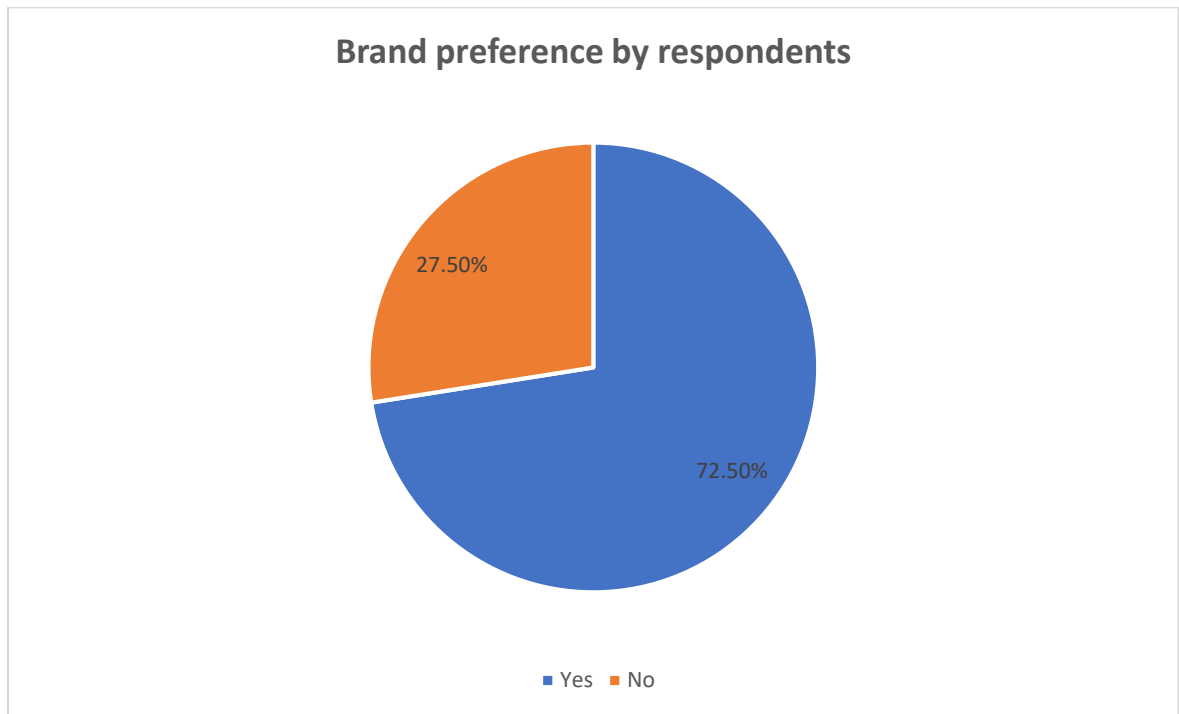


Figure 5: Brand preference by Respondents

During conversation with the respondents I asked about any brand preference towards the plasma products while prescribing to the patients. All responded but some had not replied about brand. 72% responded that they prefer brand and 28% are not looking for brand, they just only depend upon quality & minimum side-effects, they are totally focused on prescribing efficacious treatment to the patient .

4.1 Name of the most popular brand:

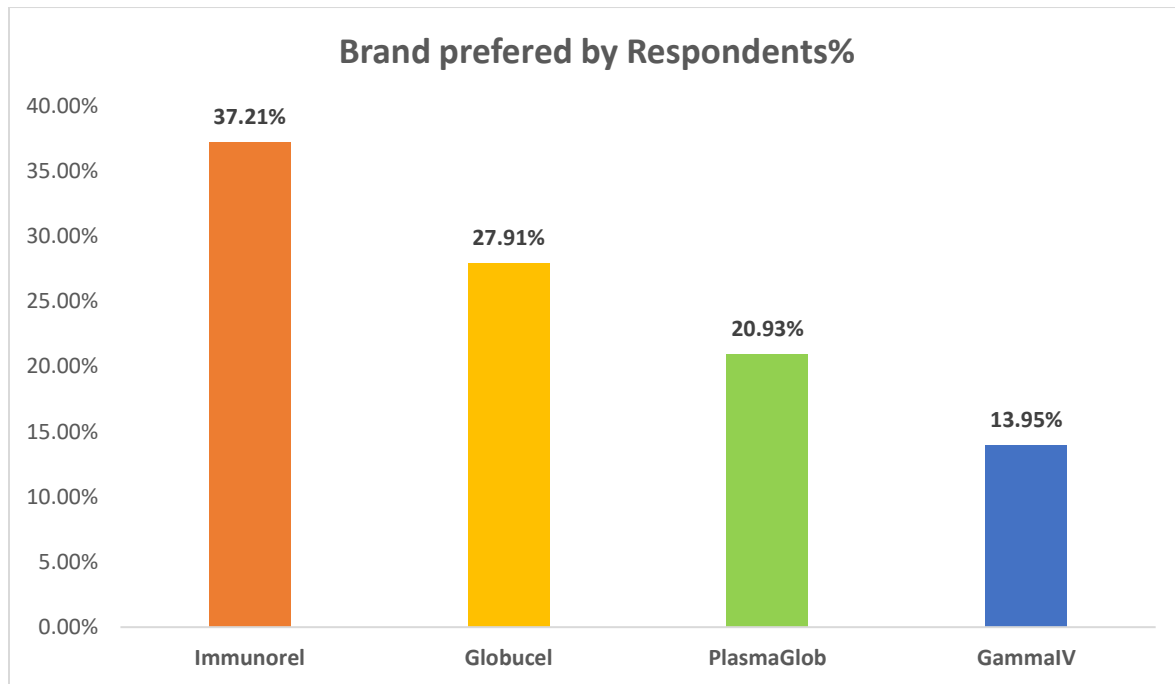


Figure 6: Brand preferred by respondents%

These are the brands which is established in the market in between medical fraternity becuz of various reasons. Reliance, Intas and PlasmaGen are the major player in the market with their products .

5.Attributes to be considered while prescribing the plasma products:

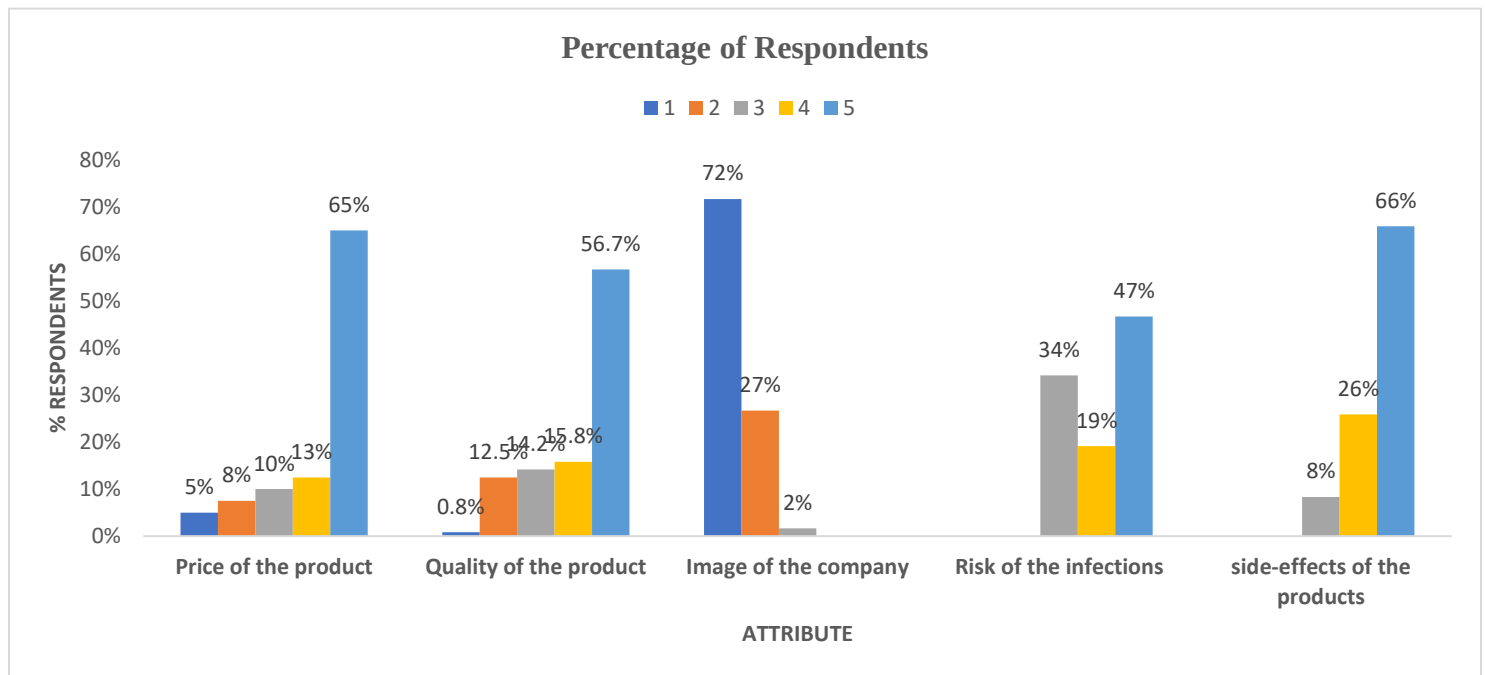


Figure 7:percentage of respondents towards various attributes

For the government doctors the cost of the product is the important attribute while prescribing the plasma products where as for the private practice doctors the cost is least important or somewhat important factor. Image of the company is least important and somewhat important factor while prescribing the plasma products .

The respondents considered risk of viral infections and all type of blood borne infections as somewhat important and most important while prescribing the plasma products. As the currently available products are highly purified and less immunogenic most of the respondents considers the side effects of the products as somewhat important .

Due to the high cost of the plasma products some of the patients do not adhere to the prescribed therapy. As these plasmas are prescribed in some limited indications so the respondents consider requirements of the patients as the most important attribute while prescribing the plasma products. Cost of the product (65%), Quality of products (57%) and side effects of products (66%) were the main attributes while prescribing the plasma products .

6.Percentage of doctors satisfied with the performance of available plasma products in the market.

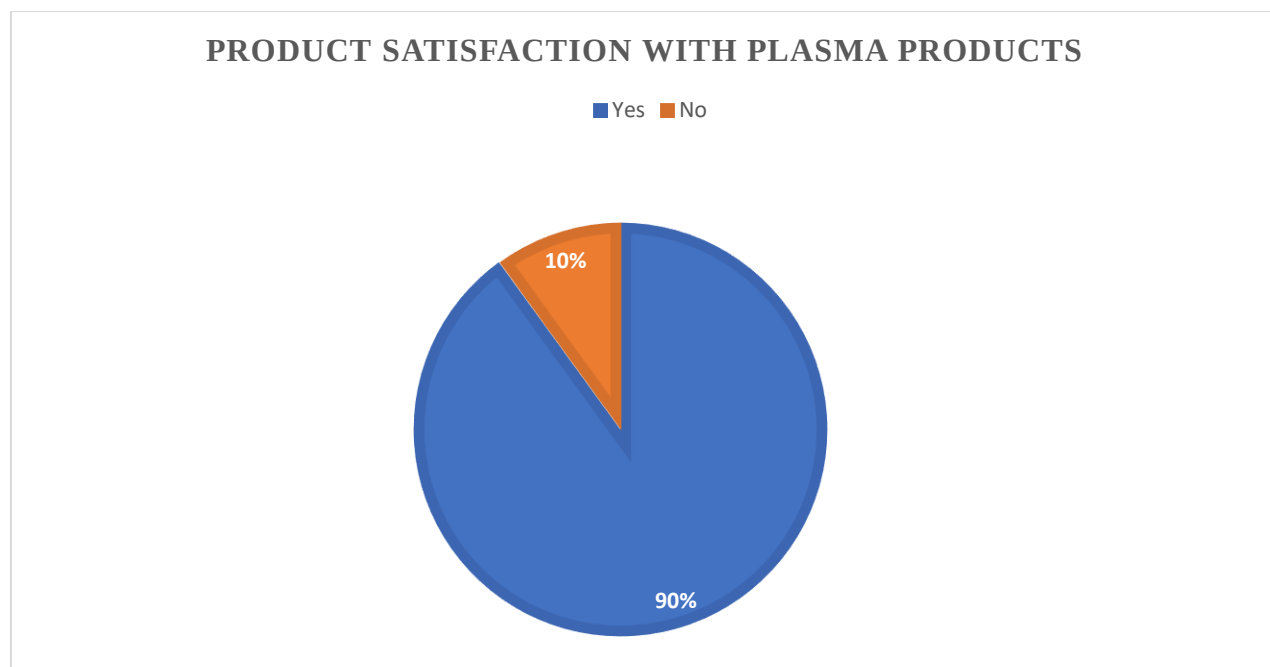


Figure 8:product satisfaction with plasma products

About 90% of the respondents are satisfied with the performance of the available plasma products in the market where as about 10% of the respondents are not satisfied with the performance of the available products in the market. Those who are not satisfied will be looking for the various benefits in the products like cost, risk of the infections, side effects of products .

6.1 Benefits that unsatisfied respondents are looking for

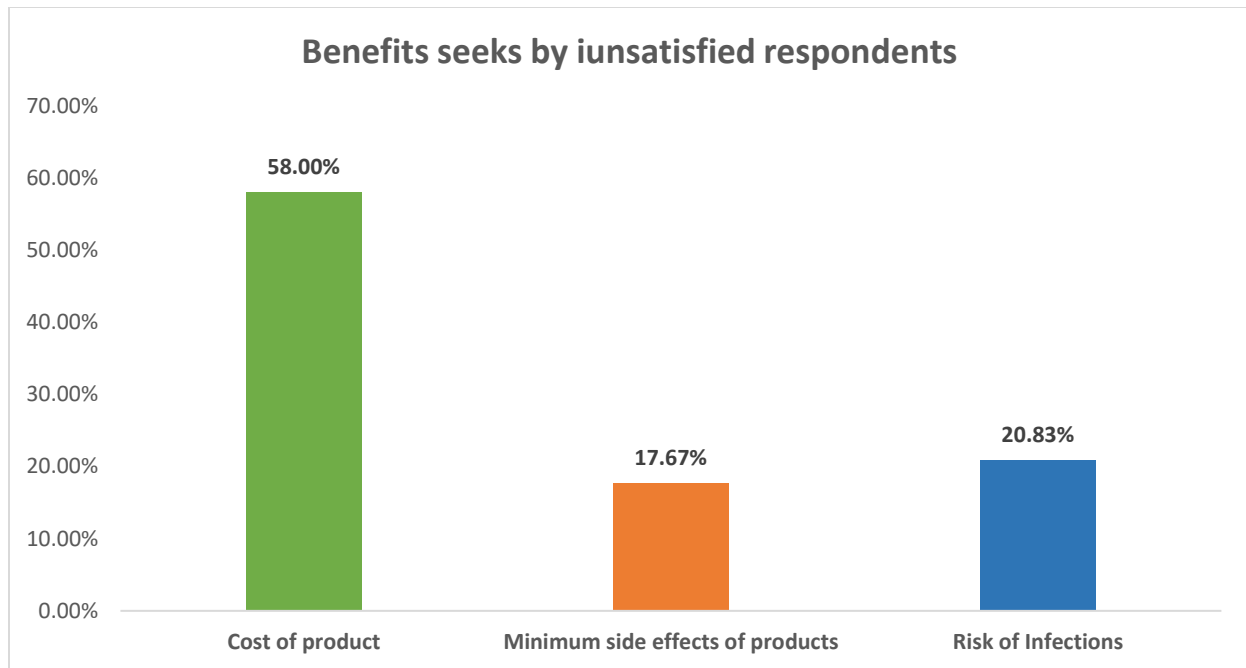


Figure 9:Benefits seeks by unsatisfied respondents

10% of the respondents are not satisfied with the performance of the available products in the market and they were looking for the benefits like risk of infections and minimum side effects of products followed by the cost of products .

7.Problems considered while prescribing plasma product:

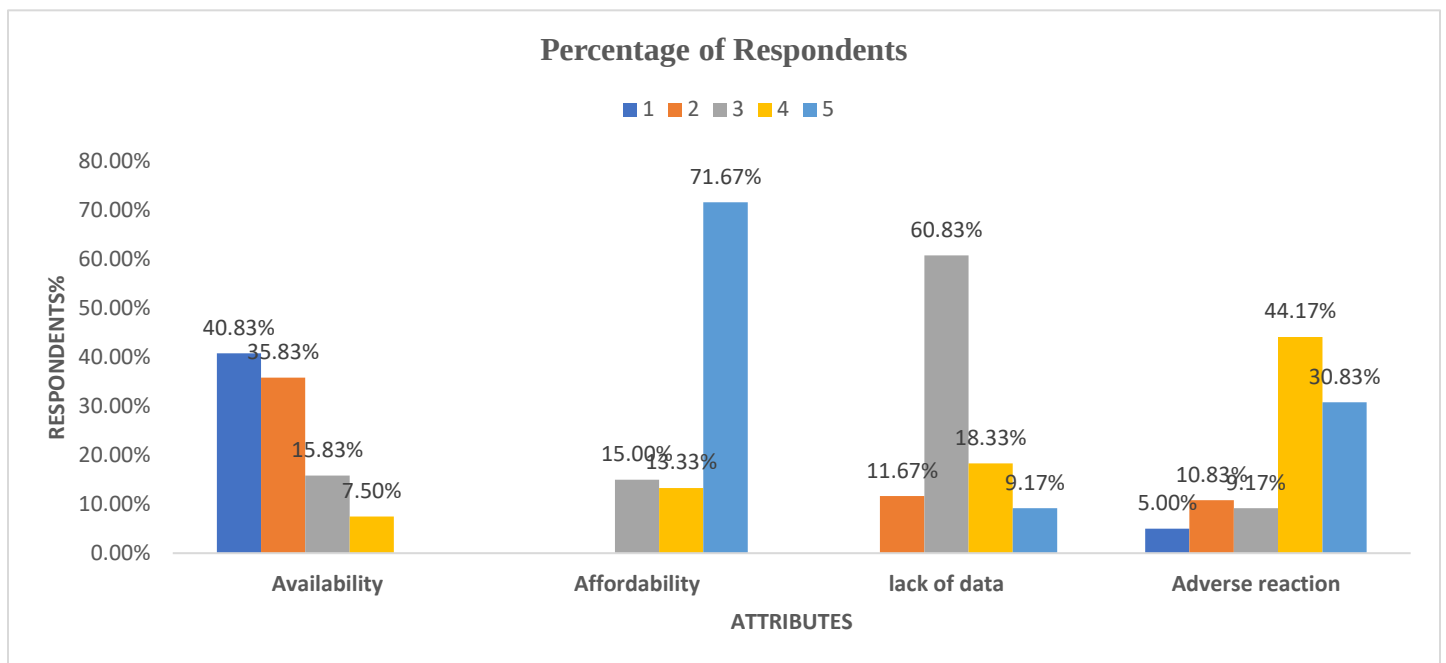


Figure 10: Problem considered while prescribing plasma products

(41%) respondents accepted that availability is not the major problem in the prescription of plasma products. Affordability (72%) is the major problem in prescribing the plasma products and about (72%) respondents accepted that lack of data for special indications are not available and (44%) respondents accepted that adverse /Anaphylactic reactions occurs in different diseases. In recent years the use of plasma products increased in off label indications .

Findings from Doctor's Response

- 100% of the respondent interviewed prescribe the plasma products to their patients. These 100% of the respondents comprises of the doctors who were prescribing all the plasma products like human albumin, IVIG and clotting factors to their patients .
- The 45% of the prescriberswho prescribes the plasma products to 10-25% of their Patients comprises of the physicians,Hemato-oncologists and Intensivists .
- It was observed that the respondents were prescribing the albumin to the patients. This group comprises of physicians,pediatricians, intensivists and surgeons. Its use in current clinical replaced by the dextran and other polymer type of the volume expanders because they are easily available and less prone to the viral and other type of blood borne infections .
- The gynecologists are also using the albumin in preterm baby and to maintain the volume loss in the post-operative patients afterin obstetric surgery.
- The albumin is also used by the general surgeons in post-operative patients.
- There is the more demand for the low salt albumen in the market as this is frequently prescribed.
- About 45% of the respondents were prescribing theintravenous immunoglobulin to their patients, this percent mainly consists of general physicians, hemato-oncologists, neuro physicians.
- The Hemato oncologists mainly prescribe IVIg for ITP, all immune thrombocytopenia and AIDS related thrombocytopenia. Neuro-physicians were using IVIg in GBS, Evans Syndrome, myasthenia, stiff person syndrome and in some newer indications like dermatomyositis and demyelination .
- About 71% of respondents were not prescribing clotting factors to their patients. This percentage of not using the clotting factors is since doctors were using whole human blood, whole human plasma cryoprecipitate instead of specific clotting factors .
- The clotting factors are most commonly used in Hemophilia, Von Willebrand disease, Liver disease and DIC (Disseminated Intravascular Coagulation).
- The pediatrician prescribes the clotting factors in neonatal liver disease and septicemia.
- After interacting with some respondents, it was found that individuals with <1% of the normal level of clotting factors have severe hemophilia and have a higher need for substitution therapy.

- 77% of the respondents were aware of the existing brands of plasma products. Most able to recall the brand names of the plasma products.
- 72% of the respondents said that there is a well-established brand in the plasma product category.
- 39% of the respondents said that (Reliance Lifesciences) is the most popular brand of the plasma product category where as 29% of the respondents said that(Intas) is the most popular brand and 13% of the respondents said that (PlasmaGen Biosciences) is the popular brand in recent market .
- 23% of respondents are not satisfied with available plasma products in the market and they were looking for the benefits like and risk of infection followed by the cost of the products.
- Problem of cost of the product (65%),Lack of data in special indications (71%), adverse reactions (44%), were the major problems while prescribing the plasma products.

SUGGESTIONS:

- It is evident from the survey that presently, the plasma products are more prescribed by pediatricians, gynecologists and general surgeons. There is more space to capture in these segments, because competition is less in this segment, so we can create our own market place .
- A proper promotional plan should be developed with an objective of increasing awareness about the use plasma products. The promotional plan should be focused; and should demonstrate the key concerns of the target customers by organizing seminars, conferences etc. on a regular basis. The target customers should be made aware of the benefits of the plasma products .
- Brand name is one of the most important parts of positioning and it must be taken in to consideration that it can be easily recalled by doctors. The effective positioning strategy must be made so that the brand name can be recalled by doctors .
- The neuro physicians and Hemato oncologists are using these products in newer and rare indications so the plasma products should be actively promoted to these specialties of doctors. The medical literature should be provided to doctors to make them aware about the recent advances in plasma products usage in newer indications .
- The target customers should be properly identified and characterized based on heavy moderate and low users.
- Price is the important criteria for making brand successful, so price should be economical as well because many doctors rely on price factor while prescribing medication especially in government hospitals .

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