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Review Article

Pharmaceutical analysis for Novel Drug Formulation

Platelet Rich Plasma Therapy: A Quick Note for Every Health Care Professional

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Abstract: Blood is a fluid connective tissue consisting of cells and plasma. The plasma occupies 55% of blood, which is rich in immunoglobulins and proteins that have a wide range of applications in the medical field. Utilizing this plasma to tackle various diseases/disorders is called plasma therapy. Health care professionals require basic and quick knowledge of plasma therapy. It was attempted to bring a quick guide about plasma and its effective utilization in tackling deadly diseases. The plasma is being used in several issues like tissue regeneration, wound healing, scar revision, skin rejuvenating effects, alopecia, and now for the coronavirus disease (COVID-19). The Platelet Rich Plasma (PRP) has been used to heal wounds and illnesses. The theory behind PRP therapy is that it will induce the body to develop new, healthy cells that facilitate healing. Plasma contains important components like enzymes, antibodies, coagulation factors, albumin proteins, and fibrinogen. As PRP is rich in the proteins and antibodies, it is used for rare chronic therapies and many severe health problems. PRP therapy is gaining attraction by many health professionals as it is a safe, effective, efficient, and easy approach in procuring, preserving, and therapy. This review summarises and highlights the principle, techniques, method of preparation of PRP, convalescent plasma therapy, and plasma-derived therapies for patients with immunodeficiency or infected with infections to fight pathogens and get cured effectively in a short time.

Keywords: plasma, platelets, health, immunity, treatment

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1. INTRODUCTION

Plasma is the major fluid in the body, that takes up more than half (55%) of the total amount. Plasma is a bright yellow fluid and its key function is to carry foods, hormones, and proteins to certain areas of the body that require them.[1] Along with essential ingredients, plasma contains oxygen, salts, enzymes, anticorps, coagulation factors, albumin, and fibrinogen proteins[2]. Owing to these contents, plasma therapy will benefit patients recovering from fire burns, anesthesia, injuries, and other medical conditions and save their lives. For rare chronic therapies like Hemophilia and Autoimmune disorders, the antibodies and proteins in plasma are much helpful. People with AB blood groups have the highest demand for collecting plasma, as only 2 in 50 persons have this blood group.[3] Plasma serves to disperse heat across the body and preserve homeostasis .[4] Immune plasma refers to plasma obtained from organisms, following infection resolution and antibody production. Passive antibody therapy by transfusion of recovering plasma may avert clinical contagion or dull clinical harm in persons with fresh pathogen acquaintance.[5] Antibody therapy may also be adopted for the treatment of patients with signs of varying severity. Passive antibody therapy, though, is more successful, it is performed prophylactically or utilized early after symptoms started. Passive antibody treatment was in operation for more than ten decades. The active mediators are antibodies in contradiction of interest-bearing target pathogen. Passive antibody therapy today trusts primarily on joint immunoglobulin provisions which contain high antibody concentrations. In comparison, plasma has been used in epidemics when there is less time or economic to generate preparations for immunoglobulins.[6] There are many examples, both historical and modern, of which convalescent plasma was effectively used as a prophylaxis post-exposure (E.g., hepatitis, mumps, polio, measles, rabies) and/or diagnosis of a multitude of infectious diseases (E.g., influenza, Argentine hemorrhagic fever, SARS-CoV, MERS, Ebola, and even COVID-19). Platelet-rich plasma (PRP) is extracted from the blood by obtaining a drop of venous blood, inserting it in a special tube, and centrifuging the blood about 3000 rpm for 3 min in a centrifuge.[7] This separates the whole blood into its elements, including Cells (Red blood cells [RBC]) and the non-cellular fluid (plasma). The intermediate layer is PRP, which comprises extremely enriched specialist chemicals named growth factors. These growth factors derived from platelets, transforming the β-growth factor, and growth factor for the vascular endothelial cells. Such factors communicate with the local cells and give signals triggering many events including cell division and migration. The fundamental concept behind PRP injection is to administer large doses of growth factors to an injured region, aiming to induce a curative reaction and reduce tissue inflammation. Whole blood injection can induce the same reaction to some degree but a smaller extent. PRP has been used in orthopaedic, and cosmetic surgeries to facilitate recovery.[8] In the last 5 years, PRP has been recognized as having the ability to heal evaluating tendons, ligaments, and tissues in both recurrent and severe musculoskeletal injuries. The technique is attracting broad public coverage because it has been implemented with retired athletes as early as possible with efforts to restore them to action.

2. *PLASMA THERAPY*

The plasma therapy has further divided into the following varieties

2.1. PLATELET-RICH PLASMA THERAPY

PRP injections are used for treating broken tendons, tendinitis, muscle injuries, pain associated with arthritis, and joint injuries.[8] Also, they are more common for cosmetic procedures. For example, dermatologists and hair-replacement specialists use PRP injections to treat a form of androgenic alopecia, which affects both men and women and some dermatologists treat skin-related issues on the face with PRP.

2.2. PREPARATION OF PRP

PRP is found from a sample of the blood of patients collected during diagnosis. A 30 cc venous blood can produce 3-5 cc of PRP based on an individual 's baseline platelet count, the system used, and the procedure used.[9] Blood drawing happens when anticoagulant (citrate dextrose A) is applied to avoid platelet activation preceding to its use. So, a specific tool called the table-top cold centrifuge' is adopted.

2.3. PRINCIPLES AND PROCEDURES OF PRP PREPARATION

PRP is made by centrifugation, the acceleration force is modified based on different basic gravity to sediment those cellular constituents. There are plenty of ways to train for PRP. It can either be prepared using the PRP method or Buffy-coat process. Initial centrifugation to discrete red blood cells (RBC) is followed in the PRP cycle. Second centrifugation of the platelets is to concentrate, suspended in the smallest final. Initially, whole blood (WB) is stored in tubes containing anticoagulants.[10] The first step is to isolate RBCs of the remaining WB volume are carried out at steady acceleration. Later the first rotation steps, the WB splits into three layers (the upper layer the intermediate thin layer [which contains mainly platelets and WBC], and the lower layer (consists of RBCs). The upper and intermediate layers are transferred to a vacuum sterile tube for pure production PRP (The P-PRP). The whole layer of intermediate coat and lower layer are transferred for the development of leukocyte rich PRP (L-PRP). The second step of the spin is then executed.[11] The second spin 'g' will be adequate to assist in the creation of soft pellets at the foot of the tube. It eliminates the upper side of the volume mainly composed of PPP (platelet-poor plasma). Pellets are homogenized to form the lower 1/3rd (5 ml) of PRP. A Buffy-coat contains a high leukocyte concentration. A very strong one Buffy coat thin layer may be formed from a small capacity of WB (10 ml). The challenge is to separate this thin buffy coat layer, which mainly contains white blood cells (WBCs) and platelets, from the underlying RBC layered by differential centrifuge.

2.4. PRP PREPARATION METHOD

2.4.1. ROUTINE CENTRIFUGATION METHOD

The important steps involved in the preparation of PRP preparation.[12]

- WB of acid citrate dextrose (ACD) in tubes are obtained by venipuncture
- Do not cool the blood before or after the separation of the platelets at any time.
- Blood centrifuge uses a 'soft' spin.
- Moves supernatant plasma with platelets (without anticoagulant) into another sterile tube.

- Centrifuge tube to receive a platelet concentrate at a higher rate (a quick spin).
- The downside 1/3rd is PRP, and the upside 2/3rd is platelet-poor plasma (PPP).
- Remove PPP and hang up the platelet pellets in a minimum plasma quantity (2-4 ml) by shaking the tube gently.

2.5. BUFFY COAT METHOD

This method needs the following steps.[13]

- WB should be processed, before centrifugation, at 20°C to 24°C.
- WB centrifuge at 'high' velocity.
- Due to its density, three layers are formed: the bottom layer composed of RBCs, the middle layer composed of platelets and WBCs, and the top layer of PPP.
- Supernatant plasma is removed from container tops.
- The Buffy-coat coating is moved to another sterile pipeline.
- To separate WBCs or use low-velocity centrifuge leukocyte filtration.

There is no such thing as Consensus as to whether or not to cause platelets before application, and which one agonist with. Some researcher's trigger thrombin or calcium platelets while others use platelets beforehand with no activation, suggesting better results received.

2.6. CONVALESCENT PLASMA THERAPY

Convalescent blood products (CBPs), taken from a patient who has survived an earlier infection and earned humoral immunity. Pathogen accountable for the disease by extracting whole blood or plasma is a potential source of specific human antibodies. CBP transfusion can counteract the pathogen and in time contributes to blood circulation eradication.[14]

- Convalescent whole blood (CWB), convalescent plasma (CP) or convalescent serum (CS)
- Collective human immunoglobulin (Ig) for IM or IV administration
- High-title patient Ig
- Monoclonal or polyclonal antibodies

CP has been the focus of growing concern, especially in the midst of epidemics of great scale. The apheresis plasma is currently the preferred therapeutic tool as a greater amount is obtained each session, the likelihood of more regular donations, and the lack of an effect on the donor's haemoglobin due to the reinfusion of their RBCs. Recruitment of donors living in areas where an epidemic has broken out may offer the added value of giving specific passive immunity opposite to the local infectious agent that has been artificially acquired, whereas CBP supplied from other regions may be less active due to (possible) strain differentiation of the pathogen concerned. Nonetheless, it can be difficult to classify, pick, and retain potential donors, as convalescent subjects must also follow donor selection requirements, in compliance with national policies and standard procedures. However, as indicated by the World Health Organization (WHO), due to the possible value of the treatment, certain donor selection criteria, while intended to protect the donor's health, maybe relaxed. Notably, the use of pathogen inactivation may guarantee additional protection and therefore endorse less stringent requirements for selection.[15]

2.7. SCIENTIFIC UNCERTAINTIES AND LIMITATIONS REGARDING THE CONVALESCENT PLASMA USE

While its effectiveness and safety have not yet been thoroughly established, treatment with CP may be a viable choice in the treatment/prophylaxis of many infectious diseases, both in combination with other drugs/preventive measures and as the only therapy when there is no possible medication.[16]

2.8. DRAWBACKS OF CP TRANSFUSION

However, some problems still need to be discussed in evaluating the advisability of introducing a large-scale CP transfusion program.[1] The lack of high-quality research (i.e., randomized clinical trials) The risk of transmitting pathogens to transfusion service workers (E.g., handling laboratory specimens from contaminated pre-transfusion testing recipients) The need for advertising: Case-fatality levels in CP studies would be affected not only by the risk factors of patients but also by the particular supportive care offered by clinical centres. Immunotherapy with monoclonal antibodies may be highly effective. Many health care workers moved to Europe or the United States received CP and survived, but also benefited from experimental therapies and adequate supporting treatment. The risk of other transfusion-borne infections (E.g., human immunodeficiency virus, hepatitis B virus, Hepatitis C virus, and Syphilis) cannot be eliminated in endemic areas and pathogen control technologies can play a key role in ensuring safe transfusion of CPs.

2.9. PLASMA-DERIVED THERAPIES FOR IMMUNODEFICIENCY

Plasma-derived therapies replace missing or deficient proteins that allow people to lead healthier and more successful lives. Patients who rely on these therapies typically need daily infusions or injections during their entire lives. Plasma protein therapy treating diseases and disorders are called rare diseases because they affect a fairly small percentage of the population; most are chronic, inherited disorders.[18]

2.10. IG REPLACEMENT THERAPY

This therapy is a lifelong, life-saving procedure that needs to be performed periodically. It is important not to skip or neglect the treatment as each treatment only offers temporary protection against infection. Another kind of plasma-derived therapy is specifically used to treat hereditary angioedema (HAE), patients. For people living with this disease, there is a missing or malfunctioning part of the immune system called the *C_1 esterase* inhibitor (C_1-INH), and C_1-INH concentrate derived from plasma can be administered to avoid and cure the symptoms of HAE-related inflammation.[19]

2.11. ROUTES OF IG REPLACEMENT THERAPY

IG replacement therapy is either delivered subcutaneously (sc) or intravenously (iv) as an injection.[20]

2.12. IV ROUTE

Infusion of IG straight through a vein into the bloodstream. The main benefit of using this route is that it is possible to prescribe a more dose of IG compared with the SC route and that care only has to be given every 3 to 4 weeks. This can be given as iv infusion which takes 2–4 h to administer, and needs hospitalization for its administration. This can also be provided at home by a nurse or a qualified carer. Slight side effects can happen during or after IV infusions.

2.13. SC ROUTE

Use either a handheld infusion pump (syringe driver) or rapid push technique, injection of IG is just below the skin of the upper arm, belly, thighs or buttocks. The rapid push technique is an easy way to move the IG under the skin using a syringe at a convenient pace.

2.14. SIDE EFFECTS OF IG THERAPY

Most patients with IG replacement therapy will not experience significant side effects. Many patients may however report the following. [21]

- Cranks
- Lightheaded, tired or sick
- Fever
- Chills
- Feeling sick
- Itching
- Skin tingling
- Pains at the joint
- Quick heartbeats

These side effects are less frequent with the administration route of SC than the route of IV. Nonetheless, SC infusions at the site of injection may lead to some swelling and pain. Some side effects lead to slowing the rate of infusion and maintaining congenial hydration before and during treatment (intake of alcohol must be limited to prevent dehydration).

2.15. APPLICATIONS OF PRP

Plasma therapy is being successfully used for many years, few are highlighted in table 1.

Table 1. Milestones of plasma therapy for various diseases

Year	Disorder/disease	References
1953	Primary immunodeficiency disease[22]	(22)
1970	Hemophilia A[23]	(23)
1970	Hemophilia B[24]	(24)
1980	Alpha-1 antitrypsin deficiency [25]	(25)
1995	Kawasaki disease[26]	(26)
1996	Chronic inflammatory demyelinating neuropathy (CIDP) [27]	(27)
1996	Idiopathic Thrombocytopenic purpura (ITP) [28]	(28)
2005	Von willebrand disease[29]	(29)
2008	Hereditary Angioedema[30]	(30)
2009	Antithrombin III Deficiency [31]	(31)
2009	Influenza virus[32]	(32)
2013	Cancer[33]	(33)
2014	Ebola virus[34]	(34)
2015	Pulmonary disease[35]	(35)
2019	Parkinson's disease[36]	(36)
2019	COVID-19[37]	(37)

2.16. Latest updates on platelet rich plasma therapy for COVID

It was demonstrated clinic features and therapies of COVID-19 patients with PRP therapy and compared with traditional Chinese medicines[38]. The assortment, manufacturing, pathogen inactivation, and backing, with a focus on COVID-19 was explained by Focosi *et al*[39]. Skendros *et al* explored how complement relates with the platelet extracellular traps using COVID-19 specimens[40]. Elizabeth *et al.*, explored that Neutrophil extracellular traps initiates from chromatin unconfined to immobilize pathogens and can trigger immunothrombosis in COVID-19 Acute Respiratory Distress Syndrome[41]. Xie *et al,* reviewed 58 cases of COVID-19 pneumonia within 48 h of admission to the ICU can lessen the use of motorized aeriation, curtail the hospital stay, indorse the early retrieval, and mend the actual handling of patients to attain noteworthy clinical usefulness[42].

3. CONCLUSION

The information in this article will give quick information about platelet-rich plasma (PRP), its composition, preparation, and its utilization in tackling infections. Platelet-rich plasma (PRP) therapy is a simple, economical, and feasible in the treatment of various clinical issues in the field of dermatology, dentistry, orthopedics, surgery, ophthalmology. Although experience and clinical data, dose are important factors to be optimized for such therapies. Additionally, PRP therapy is implemented to tackle influenza, SARS-CoV, MERS, Ebola, and even COVID-19. Even after having many reported positive effects of using PRP, many studies required to prove its safety and standardization of PRP.

4. AUTHORS CONTRIBUTION STATEMENT

All authors Yedire Bharath Kumar, Hindustan Abdul Ahad, Chinthaginjala Haranath, Gopavaram Sumanth, Durga Sumanth Pasupuleti and Srilekha Surapa Reddy, all authors involved in the collection, editing, and approved the final manuscript.

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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