Received: October 13, 2026
Accepted: October 26, 2026
Published: November 27, 2026

Acad Med J 2026;6(3):237-240
UDC: 615.382.03
Commentaries

PLATELET-RICH PLASMA (PRP) AS AN ORTHOBIOLOGIC TREATMENT – WHAT DO WE KNOW SO FAR?

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In the past decades, platelet-rich plasma (PRP) has gained enormous popularity in regenerative medicine, not only as a hair loss and skin-rejuvenation (anti-aging) treatment option but, most importantly, as a treatment option for tendon, ligament, muscle and joint injuries, orthopedic post-surgical healing, and osteoarthritis[1].

Core components of platelet-rich-plasma (PRP)

Platelet-rich plasma is a biologic, autologous blood-derived concentrate obtained from the patient's blood[2,3]. The patient's blood undergoes centrifugation to isolate and concentrate the plasma, platelets, platelets-derived growth factors, white blood cells and other active biomolecules, and remove the red blood cells[2].

Blood is a connective tissue that contains cellular elements like red blood cells, white blood cells and platelets as well as a fluid part, the plasma. The plasma is mainly composed of water, proteins, hormones, electrolytes, nutrients, dissolved respiratory gases (oxygen and carbon dioxide), and metabolic waste. Water has the role of a transport medium. Plasma contains core proteins such as albumin, globulins (immunoglobulins) and fibrinogen. Albumin has the role of regulating the fluid balance and transporting vital biomolecules. Immunoglobulins support the body's defense, and fibrinogen assures coagulation[4].

Platelets or thrombocytes are blood cells that play a role in hemostasis. They are in charge of the primary hemostasis, or the hemostatic clot formation as a first response of the body to injury, followed by the secondary hemostasis, or mesh formation[5]. In addition, platelets contain bioactive molecules as growth factors, chemo- and cytokines, as well as proinflammatory mediators (prostaglandins, prostacyclins, histamine, thromboxane, serotonin and bradykinin). The biomolecules in the platelets are involved not only in hemostasis, but also in fibrinolysis, angiogenesis and proliferation, initiating the remodeling phase of the tissue repair process[3].

White blood cells or leukocytes have a role in the immune response. Neutrophils initiate the inflammatory phase. Monocytes and macrophages are responsible for "cleaning" the necrotic tissue first, followed by the release of growth factors from the macrophages for tissue repair. Lymphocytes are responsible for the adaptive immunity or building the immunological memory[2].

Red blood cells or erythrocytes are crucial for transportation of oxygen and carbon dioxide to and from the cells ensuring tissue oxygenation and normal cell metabolism. They are also responsible for maintaining the pH of the blood, normal blood viscosity and blood flow[4].

Erythrocytes are in the blood but are excluded from the PRP formulation. They are separated and eliminated through the process of centrifugation of the blood. The main reason for eliminating the red blood cells from the plasma are their cytotoxic effects and their rather

harmful than beneficial properties at the injured site. Under oxidative stress, the hemoglobin from red blood cells releases free iron and accumulates reactive oxygen species (ROS), an oxygen containing free radicals, leading to cell death and tissue damage[2,8].

Mechanism of action of platelet-rich plasma

The mechanism of action of PRP is based on a few physiological processes that complement each other. After the patient's blood is centrifuged, the plasma is concentrated and enriched with platelets. The platelet concentration in the plasma is above the baseline. Although the mechanism of action of PRP continues to be studied (it is not entirely understood), a few pathways or processes have been identified as essential for healing and tissue repair, starting with hemostasis. After the PRP injection at the injured site takes place, platelets begin to adhere and aggregate. Platelet adhesion promotes hemostasis and cell recruitment and is the first step in vascular injury healing. It assures blood clot formation, which prevents hemorrhage and later formation of a temporary extracellular matrix that allows injury healing[3,6].

Leucocytes from the PRP formulation have their own role in the tissue repair process, participating in the inflammatory phase. Leucocytes are responsible for immunomodulation and inflammation pro-resolving activities[2,3]. Neutrophils, as leucocytes, are the first line of defense at the injured site and are known for their phagocytic activity. Due to the short life span of neutrophils, macrophages are next in line involved in phagocytosis and debridement as well as inflammatory regulation[2,3,7]. In addition, macrophages contribute to the recruitment of fibroblasts and endothelial cells by promoting angiogenesis[2]. Lymphocytes, more precisely, T and B lymphocytes, have their own role in immunomodulation and anti-inflammatory processes. Lymphocytes are responsible for adaptive immunity and immunological memory[2].

Alpha granules from platelets have a significant role in the process of tissue repair. Alpha granules contain 284 proteins that participate in hemostasis, angiogenesis, tissue regeneration and inflammation. Fibrinogen, von Willebrand factor, prothrombin, and other coagulation factors, as well as membrane glycoproteins and receptors, and fibrinolytic proteins (plasmin, plasminogen, and antithrombin) participate in hemostasis[2]. Most importantly, alpha granules contain growth factors. Due to enhanced platelet concentration, PRP has 3 to 5 times higher growth factor concentrations than baseline levels. The release of growth factors from alpha granules (VEGF-vascular endothelial growth factor, PDGF- platelet-derived growth factor and TGF-β-transforming growth factor beta) has a role in the regenerative phase. Platelets-derived growth factors stimulate angiogenesis and matrix synthesis, and support vascular remodeling and nutrient delivery. This is the most investigated process identified as critical for any tissue regeneration, remodeling and repair and injury healing[2,3].

Alpha granules from platelets, in conjunction with delta granules, mainly contribute to hemostasis. One role that is under-studied is the unique role of delta granules in pain processing and modulation. Delta granules, among other bioactive molecules, contain serotonin. Platelet-derived serotonin has a dual role; a pain-promoting (hyperalgesic) and pain-suppressing (analgesic) effect. The analgesic effects or the reduction of inflammatory pain is desired in any injury healing process. How platelet-derived serotonin modulates pain is not yet well understood, considering its dual role in both pain enhancement and pain suppresion[2]. Further research is needed to identify the factors that play a role in increasing the analgesic effect of PRP[11].

All of the above-described processes are interconnected, and the success of the tissue damage repair depends on each step of each process equally. In addition, wound healing and the degree of tissue repair depend on patient individual characteristics, such as the severity, type and location of the injury; level of vascularization of the injured area; ischemia; hypoxia; infection; growth factor imbalance; body's ability for regeneration; age; etc[3].

Platelet-rich plasma as an orthobiologic, and its use in orthopedic regenerative medicine

The effectiveness of PRP on the cells of the musculoskeletal system has been demonstrated in many *in vitro* and *in vivo* basic science studies. There are fewer clinical studies to support the above-statement and further research is needed[9]. More clinical trials are needed to bring insight into the method of PRP preparation, mechanism of action, dose and frequency of application, and to identify which type of PRP will achieve better clinical results in the treatment of each musculoskeletal condition[10].

Because PRP is a biological, blood-derived concentrate derived from the patient's blood, PRP preparation, composition and standardization on PRP content are crucial. PRP composition and content depend largely on the preparation method. The next vital step is having consensus on the method of PRP preparation. There are two main methods for PRP preparation: based and "buffy coat" methods. The second one produces greater concentrations of platelets[10,11]. PRP preparation is manually done, thus, the skill level of the laboratory technician as well as individual patient characteristics may contribute to the composition of the formulation[3].

To have an effective and safe biologic medication, the medication content should be well defined. This means the standard range or the number of platelets, platelet-derived growth factors and/or leucocytes should be well defined in each administered dose. Each dose of PRP should have a pre-established range or optimal concentration of the active ingredients. The physiological status of the patient and the patient's platelet count, as well as assuring that the patient does not have a growth-factor imbalance are the first steps in the standardization process. As currently indicated in the literature, the optimal platelet concentration for promoting bone regeneration should not be below 0.5-1.5x and above 6-11x the whole blood concentration[10].

Clinical consensus and clinical protocols are needed on the amount of unit dose/injection, timing of the injection, number of doses (including minimum and maximum dose per given period) and frequency of administration of PRP[12]. Standardization and protocols on indication of the PRP as an orthobiologic are needed as well. Clinical trials on the overall effectiveness and safety of PRP, as well as the effectiveness and safety of PRP for specific orthopedic conditions are needed. The level of damage of the tendon, ligament, muscle or joint injuries need to be well classified and the effectiveness of PRP needs to be investigated for each level of damage. Additionally, pre-post prospective clinical trials supported by PRP effectiveness via imaging techniques are necessary. Further studies are needed on patient mobility, pain reduction and quality of life improvement, as well as evidence for cost-effectiveness of PRP, considering that this treatment is not covered by health insurance and that patients must cover the costs.

There are additional patient-individual factors that moderate PRP effectiveness and need to be considered in the PRP treatment process. In 95% of the population, the platelet count is between 150,000 and 450,000 per μL, meaning there is great variability in platelet count in the general population[12]. Having the procedure done in the afternoon and on a full stomach after eating a meal with high fat content (the collection of blood or venepuncture) can lead to a higher platelet concentration. The use of anticoagulants and the type of anticoagulant used in PRP preparation to prevent coagulation should be another consideration[10]. High blood pressure can reduce platelet counts. Reducing the patient's blood pressure prior to PRP application can lead to an increased platelet counts. Mental and physical stress of the patient can increase premature release of platelet bioactive compounds and platelet aggregation prior to PRP preparation and administration. A diet high in saturated fats, excessive sugar, or simple carbohydrates can also induce and increase platelet aggregation. Diets high in caffeine content or quercetin (a flavonoid present in onions, apples, tea, and wine or taken via supplements) as

well as isoflavones, present in legumes, can reduce platelet activation. Medications such as nonsteroidal anti-inflammatory drugs, antihistamines, antibiotics, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants can affect the platelet function as well[12]. In summary, considering all these factors to assure a normal number and function of platelets prior to PRP preparation and administration is crucial for PRP composition and effectiveness. The role of the orthopedic specialist is not only in determining the type and the method of PRP preparation, but also ensuring that the patient's blood can produce PRP with optimal effectiveness.

Conflict of interest statement. None declared.

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