Platelet-rich plasma: Clinical use in orthopedics

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Abstract

The advances generated in the field of orthopedics, specifically in the treatment of soft-tissue injuries in the musculoskeletal system, have allowed a more favorable evolution and recovery in affected patients. The development and application of new biotechnologies, such as the use of platelet-rich plasma (PRP), have generated great interest in the area of regenerative medicine in the last decade. Being of biological origin, PRP has some advantages, one of the most important being its autologous origin, which prevents any adverse immune reaction in the patient. A disadvantage of PRP is the fact that its preparation requires obtaining a sample of blood from the patient. Furthermore, the processing of the sample usually takes between 30 and 45 min before it is ready for application. There is great inter- and intra-individual variation on platelet and leukocyte concentration obtained. As a result, efforts have been made to standardize the different formulations of PRP, using several classification scales. Multiple applications of this technology have been researched in the different areas of orthopedics; this review describes its use in some of the more frequent pathologies.

Key words: Orthopedics. Platelet-rich plasma. Tendinopathy. Osteoarthritis.

Introduction

The use of platelet-rich plasma (PRP) in health care has become more frequent, especially in the regenerative medicine field, with clinical applications in sports medicine, orthopedics, cosmetic surgery, and ophthalmology¹⁻³.

At its simplest, PRP can be described as a blood derivative which presents a concentration in the number of platelets superior to the one found in peripheral blood, which could be applied either through injection directly to the desired anatomic zone or by contact in gel form to promote tissue repair^{4,5}.

Platelets store a great number of bioactive proteins. Specifically, within the alpha granules, we can find over 30 growth factors and cytokines. Among the growth

factors present in platelets are: the transforming growth factor-beta, which promotes extracellular matrix synthesis; the platelet-derived growth factor, which presents chemoattracting activity, in addition to promoting cellular proliferation; type 1 and 2 insulin growth factor (IGF-1 and IGF-2), which participate in the cellular proliferation processes, cellular maturation, and bone matrix synthesis; fibroblastic growth factor, which is involved in angiogenesis and fibroblast proliferation; epidermal growth factor, linked to cellular activity; vascular endothelial growth factor, linked to the regeneration of blood vessels, and endothelial cellular growth factor, which is involved with endothelial cellular proliferation activity. Moreover, there are other molecules linked to alpha granules present in platelets, such as adhesion proteins (fibrinogen,

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fibronectin, vitronectin, and thrombospondin 1), coagulation factors (factor V, factor XI, protein S, antithrombin), and fibrinolytic factors (plasminogen), on top of proteases and antiproteases⁶.

As described before, PRP has been utilized as a therapeutic alternative in a wide variety of injuries and musculoskeletal pathologies. However, while there is still a large amount of information originating from basic science studies supporting the potential benefits of PRP, particularly in the acceleration of connective tissue recovery, clinical benefits have not yet translated universally into functional improvement in all cases¹.

The great variability in the composition, use, and modes of application, as well as the instruments (clinical scores and questionnaires), used to assess the clinical efficacy of PRP, make the interpretation of recent literature regarding this topic complicated. Because of this, it is important to consider different factors for the use and application of PRP. These are often mainly the platelet concentration of the sample, the number of white cells present in the sample, the presence of platelet activators (which may be exogenous or endogenous), and the application technique or clinical use⁷.

Platelet concentration and amount of white cells in the sample

Overall, two basic formats of PRP can be described according to the way they are obtained. There are preparation with the buffy coat and those based on plasma. Preparations with buffy coat, contains leukocytes and erythrocytes, while those based on plasma lack of these two blood cells⁷.

Plasma-based PRP is obtained through short periods of slow centrifugation, obtaining about 2-3 times the base platelet concentration⁷. PRP which includes the buffy coat is obtained through operating the centrifuge for longer periods and more revolutions per minute. Through this method, we can obtain larger amounts of platelets, at 3-8 times the base concentration⁷.

Pure PRP and leukocyte-poor PRP are only prepared from the plasma layer of the centrifuged blood sample, while leukocyte-rich PRP preparations also include the buffy coat. There is controversy in whether or not leukocytes are included within prepared PRP, since some studies suggest that leukocyte-rich PRP contains immune-regulatory properties, presenting pain relief in the medium- and long-term. Others believe that the presence of leukocytes reduces the ability of a

successful surgical repair because of the inflammatory process which these cells promote⁸.

According to the platelet concentration obtained, the following can be considered: when we obtain less than the normal concentration of platelets in peripheral blood, the obtained sample is denominated as poor-platelet plasma, and though in different studies, its use is considered as a control, there is not enough cellular response observed; when we obtain between 1 and 4 times more platelet concentration, positive results have been observed when applied in tendinopathies and in cell proliferation assays; when we obtain between 4 and 6 times more platelet concentration, its application has been observed to accelerate bone consolidation; while with a platelet concentration > 6 times, there is a paradoxical inhibitory effect, a type of apoptosis, or inhibitor effect on osteoblast activity⁹⁻¹⁴.

Methods of preparation of PRP

There are different commercial products (around 16) for obtaining and preparing PRP, each of these featuring their own characteristics in the obtainment process protocol according to their corresponding manufacturer. Hence, no two products are considered identical. The use of anticoagulants and local anesthetics will alter the pH of PRP, and variations in the pH of PRP have proven to affect proliferation *in vitro*; this thought to be taken into account¹⁵.

On the other hand, different "*in office*" methods have been developed for PRP preparation; that is, those procedures which are performed in the same consultation office or laboratory where the PRP is applied to the patient. An example of this procedure is one where two steps of centrifugation are performed, the first one for 5 min at 1800 rpm, which allows for the separation of the components of the blood, and later again for 3 min at 3200 rpm, accomplishing a higher platelet concentration in the PRP. With simple centrifugation, we are able to obtain 1.2 times more platelets per microliter, while double centrifugation allows us to obtain an average of 2.01 times more platelets per microliter^{16,17}.

Unlike commercial cases available for PRP gathering, in which the patient's blood sample is not exposed to the exterior, since it is handled only in a tube or syringe, with manual methods or "*in office*," the blood sample is manipulated in more than one tube and is exposed to the outside. Because of this, it is of great importance to maintain a sterile environment with the use of manual methods.

Figure 1. Platelet, activation, white classification system platelet-rich plasma. Data from DeLong, et al. 2012⁷.

Platelet activators

There are two ways of releasing the platelet's growth factors: a quick way (exogenous) and slow-release (endogenous). Quick-release can be performed through the application of thrombin, calcium chloride, calcium gluconate, or a combination of calcium chloride and thrombin, causing the release of bioactive proteins contained in the platelets in between minutes and hours. Meanwhile, endogenous release can be carried out through direct contact of platelets with the collagen of the tissue where the application occurs. For example, when PRP is applied on the knee, platelet activation is produced through contact with the articular cartilage, since platelets have specific collagen receptors on their surface¹⁸⁻²⁴. In this case, the release of the platelets' alfa granules is much slower than with the exogenous stimulus.

PRP classification

An important factor which can influence the observed discrepancy between basic research and clinical applicability is based on the significant variability which exists in the PRP products utilized²⁵. One of the proposed methods for PRP classification is through the platelet, activation, white classification system, which is based on three components: (P) absolute platelet number, (A) activation method, and (W) white cell absence or presence⁷ (Fig. 1). Another classification described is the one described by Mishra et al.²⁶ which is based on platelet number, white cell number and activation (Table 1).

Table 1. Classification of platelet-rich plasma according to Mishra, et al. 2012²⁶

	White blood cells (WBCs)	Activated?
Type 1	Increased over baseline	No
Type 2	Increased over baseline	Yes
Type 3	Minimal or no WBCs	No
Type 4	Minimal or no WBCs	Yes
	A: > 5 × Platelets B: < 5 × Platelets	

WBCs: white blood cells.

Clinical use of PRP in orthopedics

Osteoarthritis

Osteoarthritis is a degenerative disease which causes pain and disability, in addition to the fact that actually there is no treatment that can cure this pathology. Thus, different nonsurgical modalities have been employed to accomplish a positive evolution for patients. One of the alternative treatments which have increased in recent years is PRP application. Most scientific evidence regarding the use of PRP in orthopedics comes mainly from its application in the knee and hip osteoarthritis. In different studies, this treatment has proven that patients improve in their general symptomatology, joint pain (through the use of the Visual Analog Scale), and the different clinical scales used to measure the efficacy of a treatment (WOMAC, IKDC, KOOS) even in up to 12 months of evaluation²⁷. It has been proven that

PRP has clinical efficacy in the short term, similar to the use of corticosteroids or hyaluronic acid, and even its efficacy in the long term has been shown to be better than these two²⁸. Nevertheless, other studies have not reported superiority in the use of PRP over treatments with hyaluronic acid over 5 years, seeing similar results in both modalities²⁹.

Tendinopathies

Tendinopathies are the most common cause of consults as a result of aches and pains of the musculoskeletal system. The most common sites are the elbow, shoulder, Achilles tendon, and patellar tendon. In the acute stage of the pathology, early diagnosis, and the application of therapy (change in everyday activities, stretches, and anti-inflammatory medication) present a favorable prognosis. However, symptoms can be persistent in some patients. The amount of time required for a tendon to heal is long, since it is tissue with limited local blood flow³⁰. Because of this, the biological properties of PRP are able to help tendon recovery through the stimulation, proliferation, and migration of fibroblasts, as well as by increasing the vascularization and deposition of collagen³¹. To accomplish this, some authors have suggested that the application of PRP should be considered to treat chronic tendinous injuries (> 3 months) to introduce an acute inflammatory reaction, which, in turn, promotes a proliferative phase which involves collagen synthesis³².

A more recent systemic review has reported that infiltration of PRP is more effective compared to other control infiltrations (steroid, anesthetic, or placebo) since it improves the symptomatology of patients, and the application of PRP could be more effective in women than men³³. However, it is worth noting that the studied samples of patients with symptomatic tendinopathy are too small to be able to detect significant clinical differences.

Rotator cuff injuries

Rupture of the rotator cuffs are the most common causes of shoulder pain. In many cases, surgical treatment is required, which has been evolving with the use of more sophisticated implants, with the objective of accomplishing a proper repair. The ideal repair ought to have a strong initial fixation, allowing for minimum gap formation, between the injured tendon and the bone where it is inserted, and allow proper mechanical

stability until healing occurs³⁴. Rotator cuff re-rupture rate has been estimated to be around 27.3%, despite current adaptations suggested to improve tissue repair (double-row)³⁵.

The use of PRP in these types of injuries is aimed toward the improvement of the healing potential of the rotator cuff. In different meta-analyses of randomized clinical studies, as well as control cases or cohorts, no differences were found between treatment groups with and without PRP globally, when assessing the efficacy of PRP in the treatment of these injuries concerning the re-rupture rate. Nevertheless, in small or medium ruptures, patients treated with PRP showed a smaller rate of re-ruptures.

Moreover, reports state that no differences were appreciated in the assessed clinical scales in studies between patients with and without PRP treatment. Hence, concluding that, globally, PRP does not significantly improve re-rupture rates or clinical evolution in patients treated with the arthroscopic repair of the rotator cuff^{36,37}. On the other hand, other studies have found that the use of PRP does reduce re-rupture rates, in addition to improving clinical assessment scales and pain among these patients³⁸⁻⁴¹.

Due to the latter, nowadays, the use of PRP to help in the healing of tendinous injuries of the rotator cuff continues to be controversial, and can be useful in cases of small or medium injuries, but not in substantial or massive injuries of the rotator cuff.

Plantar fasciitis

This is the most common pain in the heel region, characterized by degeneration in the insertion zone of the plantar fascia over the calcaneus. Treatment with PRP has proven to be an effective therapeutic method in patients who do not respond to conservative treatment, demonstrating a similar efficacy to the use of steroids¹⁷. Moreover, PRP application usually has more lasting therapeutic effects, observing less re-infiltration rates and a reduction in surgical procedure rate compared to the use of steroids⁴².

Bone healing or delayed bone healing

The application of autologous PRP in the treatment of the nonunion of long bones with the use of fluoroscopy has been reported, where the presence of bone trabeculae through both fragments has been described in over a third of treated patients (94 patients) after 2 months⁴³.

Studies conducted in delayed diaphyseal humerus fracture healing showed that the use of PRP contributed to a faster consolidation in a significant way among these patients, without observing complications resulting from the use of PRP, and without showing a significant improvement in the functional scales of patients with regard to the control group⁴⁴.

Anterior cruciate ligament (ACL)

The inclusion of PRP in the treatment of sports-related injuries has gained significant momentum in ACL rupture⁵, under the hypothesis that the success of ACL reconstruction depends greatly on biological processes which could improve the results and ensure optimal clinical results.

Regarding the treatment of ACL injuries with PRP application, reports show that there is evidence suggesting that the use of PRP acts synergistically to accomplish a prompt maturing of the graft through evaluations by magnetic resonances. However, there is no clear difference to indicate that this aspect significantly improved the clinical evaluations of patients who underwent ACL reconstruction⁴⁵. Another aspect taken into account in this type of intervention is healing in the tunnel through which the graft goes. Concerning this particular aspect, a clear benefit has not been reflected yet when using PRP, because analyzed studies about the topic show discordant results⁴⁵.

Conclusions

There are many differences in the use of PRP, in its gathering, preparation, and application. Different classifications have been made in an attempt to standardize the obtained samples; thus, being able to assess the real reach of this biotechnology. A variety of musculoskeletal illnesses have been the object of PRP treatment, and positive clinical results have been obtained in certain ailments like osteoarthritis, and in delaying the union of different fractures, while in other pathologies like chronic tendinosis, problems have shown inconsistent results with its application. There are still several pathologies in the orthopedics area yet to be investigated to determine the best methods for obtaining, processing and applying PRP, and being able to decide on the real benefits obtained with its use.

Conflicts of interest

The authors do not have conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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