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Review

Does platelet-rich plasma have a role in the treatment of osteoarthritis?

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ABSTRACT

Platelet-rich plasma (PRP) has been generating considerable attention as an intra-articular treatment to alleviate the symptoms of osteoarthritis. Activated platelets release a host of soluble mediators such as growth factors and cytokines, thereby inducing complex interactions that vary across tissues within the joint. In vivo, PRP may promote chondrocyte proliferation and differentiation. The available data are somewhat conflicting regarding potential effects on synovial cells and angiogenesis modulation. PRP probably exerts an early anti-inflammatory effect, which may be chiefly mediated by inhibition of the NF-κB pathway, a hypothesis that requires confirmation by proof-of-concept studies. It is far too early to draw conclusions about the efficacy of PRP as a treatment for hip osteoarthritis. The only randomized trial versus hyaluronic acid showed no significant difference in effects, and no placebo-controlled trials are available. Most of the randomized trials in knee osteoarthritis support a slightly greater effect in alleviating the symptoms compared to visco-supplementation, most notably at the early stages of the disease, although only medium-term data are available. Many uncertainties remain, however, regarding the best administration regimen. Serious adverse effects, including infections and allergies, seem rare, although post-injection pain is more common than with other intra-articular treatments for osteoarthritis.

Osteoarthritis is the most common of all joint diseases and exacts a heavy economic toll due to its high prevalence in the general population and potential for causing progressive disability [1]. To date, the pharmacological armamentarium for osteoarthritis is confined to symptomatic treatments, whose goal is to diminish functional impairments and pain severity. No drugs have been proven capable of inducing clinically relevant chondro-protective effects [2].

Platelet-rich plasma (PRP) was initially used to improve outcomes of dental implant procedures. In recent years, the musculoskeletal effects of PRP have been the focus of considerable interest, most notably in sports medicine and orthopedics [3–5]. PRP is autologous plasma enriched in platelets, which can release a host of mediators and growth factors when activated by exogenous agents [6–8]. Numerous clinical trials are under way to determine whether PRP alleviates osteoarthritis symptoms when administered locally either during surgical procedures (application of PRP gel during orthopedic surgery) or as in situ injections (e.g., at sites of tendinopathy or within muscle or cartilage lesions). The results of these trials are conflicting [3,5].

Despite the wealth of recent publications, many uncertainties persist regarding the use of PRP to treat disorders of bone and cartilage [9]. A key issue is the variability in the composition of PRP [10,11]. The platelet concentration in PRP varies 5-fold across studies (from 300,000/mm^3 to over 1,500,000/mm^3). These variations are ascribable to differences in donors, collected blood volumes, agents used for platelet activation (thrombin or calcium chloride), number of centrifugations, and whether the product obtained is frozen. They obviously constitute a major obstacle

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to comparisons and also limit the validity of study results, since neither the in vitro nor the clinical results can be generalized to all PRP preparations [10,12]. In addition, widely variable intra-articular injection schedules are used, although most of them are patterned after those advocated for other intra-articular treatments for osteoarthritis (e.g., corticosteroid or hyaluronic acid), in the absence of pharmacological evidence to support this practice. Additional uncertainties stem from the presumed biological effects of PRP once introduced into the joint cavity. The release by the activated platelets of large numbers of soluble mediators such as growth factors and cytokines results in complex interactions that vary across tissues (cartilage, fibrocartilage, subchondral bone, and synovial membrane) [13]. Furthermore, PRP may exert different effects on a given tissue (e.g., presence or absence of pro-anabolic or anti-inflammatory effects) depending on the concentrations of specific mediators or on the presence of leukocytes in the preparation [7,8].

Nevertheless, this new therapeutic option may hold theoretical appeal in osteoarthritis. PRP therapy involves the direct introduction within the joint of an autologous product that may be capable of limiting the inflammatory response and promoting healing over a fairly long period [4,6]. These theoretical considerations provide a rationale for investigating PRP as a treatment for cartilage disorders, including focal lesions and the diffuse damage seen in osteoarthritis [9,14].

The objective of this article is to review current data on the use of PRP to treat osteoarthritis with the goal of better defining the potential role for PRP within the fairly limited pharmacological armamentarium.

1. What is platelet-rich plasma?

1.1. Regulatory framework

The use of autologous platelet products administered by local injection has been authorized in France since the Bioethics Law was passed on August 7, 2004, an amendment to which was introduced in 2007. The French Healthcare Product Safety Agency (ANSM, previously named AFSSAPS) defines PRP as a labile blood product prepared only from autologous material and administered only by local injection. The use of PRP can be a component of standard care. No special expertise is required to use PRP, in contrast to other platelet concentrates. When PRP therapy was first introduced in sports medicine, it was classified among performance enhancers based on its non-negligible growth factor content. In January 2011, the World Anti-Doping Agency removed PRP from the list of banned performance enhancers, and the use of PRP has been allowed by the International Olympic Committee, two changes that have contributed to the rapid development of PRP therapy in sports medicine [12].

1.2. Background, composition, and nomenclature

From a practical viewpoint, about 30 ready-to-use kits are available to facilitate the preparation of PRP from autologous blood without necessarily having to involve a hospital laboratory. The only legal requirement is the use of an accredited centrifuge that complies with European standards. Depending on the preparation method, PRPs may contain up to 10 times the normal platelet concentration, although in most studies the platelet concentration was increased 3-fold to 6-fold [15]. Once separated from the erythrocyte supernatant, the platelet concentrate is activated (with thrombin or calcium chloride) to induce the release of the largest possible amount of mediators. The panel of released mediators, or secretome, can contain up to 800 protein components [10,16].

Table 1
Platelet growth factors present in platelet-rich plasma (PRP), with their main effects.

Growth factors	Role in the joint
Transforming growth factor beta (TGFβ)	Regulates collagen production and proteoglycan synthesis Promotes chondrocyte proliferation and differentiation Stimulates angiogenesis Regulates the release of other growth factors
Hepatocyte growth factor (HGF)	Inhibits the pro-inflammatory NF-κB pathway Stimulates angiogenesis
Vascular endothelial growth factor (VEGF)	Increases angiogenesis and blood vessel permeability Promotes endothelial cell proliferation
Platelet-derived growth factor (PDGF)	Increases angiogenesis Promotes fibroblast and osteoblast proliferation and differentiation Regulates collagen production and proteoglycan synthesis
Insulin-like growth factor (IGF)	Inhibits the pro-inflammatory NF-κB pathway Stimulates osteoblast and chondrocyte proliferation and differentiation Stimulates the production of extracellular matrix
Fibroblast Growth Factor-2 (FGF)	Promotes chondrocyte and mesenchymatous stem cell differentiation Stimulates chondrocyte proliferation Stimulates hyaluronic acid production by synovial cells Increases angiogenesis
Connective tissue growth factor (CTGF)	Stimulates angiogenesis Promotes chondrocyte differentiation Promotes platelet adhesion

The main components include growth factors (Table 1), soluble mediators involved in resolution of the inflammatory response (interleukin-1 receptor antagonist [IL-1-RA], IL-4, IL-8, IL-10, arachidonic acid metabolites, and others), pro-inflammatory mediators (IL-1, IL-6, TNF, alpha-2-macroglobulin, and others), and mediators that modulate angiogenesis and coagulation [17]. Some PRPs also contain various amounts of cells belonging to the leukocyte lineage (L-PRP) and capable of producing metalloproteinases and free radicals that exert deleterious effects on the joint and may increase the risk of post-injection pain. Nevertheless, L-PRP may exert beneficial anti-microbial effects at the injection site [18]. The variability of the cell composition of PRP has prompted the development of an international classification system, known as PAW [19] and based on three characteristics: the absolute platelet count, rated from low (P1) to high (P4, more than 4-fold the normal count); the manner in which platelet activation is induced; and the presence or absence of white blood cells. When comparing the results of clinical studies, the PAW classification must be taken into account to avoid drawing incorrect conclusions.

1.3. Precautions for use

No absolute medical contraindications to the use of PRP therapy have been identified [3]. The use of autologous blood to prepare PRP eliminates all risk of incompatibility and of transmission of blood borne microorganisms [15]. However, few studies have assessed changes over time in PRP contents depending on storage duration and conditions (freezing) [10]. In addition, as PRP contains growth factors, which may have effects on carcinogenesis, an often cited precaution consists in avoiding PRP injection in the vicinity of malignant or dysplastic tissues. Furthermore, non-steroidal anti-inflammatory drugs inhibit platelet function and consequently should not be applied near or at the injection site within 48 hours to 1 week of the injection [20].

The absence of reported serious adverse events may seem reassuring, given the broad spectrum of situations in which PRP is