Platelet Rich Plasma in Orthopaedics: A Review

Vivek Mahajan

Abstract

The social impact of bone and cartilage pathologies entails high costs in terms of therapeutic treatments and loss of income. For these reasons, the trend in research is now moving towards preventive interventions and therapeutic solutions that can lead to an enhancement of tissue regeneration and the reduction of degenerative mechanisms. Orthopaedic surgeons have always sought means to use biological solutions to promote healing and regeneration. This article introduces the reader to PRP therapy and reviews the current literature on this emerging treatment modality. In summary, PRP provides a promising alternative to surgery by promoting safe and natural healing.

Keywords

Cartilage, platelet-rich plasma, growth factors.

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Introduction

In orthopaedics, the trend of the research is now going towards preventive interventions and therapeutic solutions that can lead to an enhancement of tissue regeneration and the reduction of degenerative mechanisms. Recently the idea of “biological solution for biological problems” has lead to the development of less invasive procedures and accelerated treatments that in general reduce morbidity while enhancing functional recovery.[1] One interesting

therapy is platelet-rich plasma (PRP) that can be defined as the volume of the plasma fraction from autologous blood with platelet concentration above baseline (200000 platelets/μl).[2-4]

It is well known that platelets have many functions beyond simple hemostasis; platelets contain many important bioactive proteins and growth factors, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and others. These factors when secreted, regulate key processes involved in tissue repair, including cell proliferation, chemotaxis, migration, cellular differentiation, and extracellular matrix synthesis.[5-7] (table 1)

Growth Factor	Function
Platelet-derived growth factor (PDGF)	Stimulates cell replication Promotes angiogenesis Promotes epithelialization Promotes granulation tissue formation
Transforming growth factor (TGF)	Promotes formation of extracellular matrix Regulates bone cell metabolism
Vascular endothelial growth factor (VEGF)r	Promotes angiogenesis
Epidermal growth factor (EGF)	Promotes cell differentiation and stimulates re-epithelialisation, angiogenesis and collagenase activity
Fibroblast growth factor (FGF)	Promotes proliferation of endothelial cells and fibroblasts Stimulates angiogenesis

Table 1 Growth factor chart

The rationale for topical use of platelet-enriched preparations is to stimulate the natural healing cascade and tissue regeneration by a "supra-physiological" release of platelet-derived factors directly at the site of treatment. When PRP begin to work, the local tissue which is in contact with this preparation benefits from the particular actions of growth factors, able to interact with each other and individually with cell surface receptors and with different extracellular matrix proteins. Growth factors mediate the biological processes necessary for repair of soft tissues such as muscle, tendon and ligament following acute traumatic, or overuse injury, and animal studies have demonstrated clear benefits in terms of accelerated healing.[8,9]

There are various ways of delivering higher doses of growth factors to injured tissue, but each has in common, a reliance on release of growth factors from blood platelets. Platelets must be activated in order to release growth factors. For PRP-gel preparations platelets are normally activated by thrombin (autologous or from animals), Calcium Chloride and pro-coagulant enzyme i.e. Batroxobin (Platelex, Regen Lab, Mollens VD, Marrowstim – Biomet) which works as a fibrinogen cleaving enzyme inducing a rapid fibrin clot formation. PRP solutions injected directly for topic treatments are activated by local thrombin.[10] In general, the amount of growth factors delivered is not necessarily proportional to the platelet count, because of the high variability of growth factors contained in platelets among individuals.[11,12] However studies have shown that clinical efficacy of PRP preparations can be expected at minimum 4 to 6 fold increase of platelets count from baseline value.[13-15] Final bio-availability growth factors is also dependent from extremely high sensitivity of platelets to process induced stress, from blood extraction to PRP gel preparation; furthermore the kinetic and release of growth factors from different PRP preparation can vary, even if it is still unclear if it can be clinically relevant.[10]

PRP can be obtained from a simple blood extraction using the kit provided by the manufacturer. Once the blood is collected it will undergo a centrifugation process that will produce PRP. Several systems are available to prepare the PRP and the platelet gel: however many differences exist between commercial PRP products. For scientific evaluation of platelet rich plasma efficacy in clinical studies a standardization of different PRP preparations is warranted. Dohan Ehrenfest et al proposed a classification in four categories, depending on leucocyte and fibrin content of PRP: leucocyte poor or pure platelet rich plasma (P-PRP), leucocyte and platelet rich plasma (L-PRP), leucocyte poor or pure platelet rich fibrin (P-PRF) and leucocyte and platelet rich fibrin (L-PRF).[16] Products have been evaluated according to key parameters: preparation kits and centrifuge (size and weight of centrifuge, duration of procedure, cost and ergonomy), platelets and leucocyte (volume, collection efficiency and preservation and fibrin concentration (concentration, density and polymerization type). They concluded that the world of platelets concentrates for surgical use is actually a jungle of unclear products and we agree with them that a clarification is the first step in defining any clinical and biotechnological applications for each technique.

Current Literature

Initially used as "platelet concentrate" in transfusion medicine to treat hemorrhagic conditions secondary to thrombocytopenia, acute leukaemia or severe blood loss after surgery, the use of blood derived products (fibrin glue) as wound sealant and stimulus for wound healing was started 40 years ago.[17] It was then first introduced by Ferrari et al in 1987 in open heart surgery to decrease bleeding.[18] Consequently the use of platelet concentrate to replace fibrin glue and improve healing was described by Whitman.[19] Later this therapy enjoyed a great increase in popularity because of the versatility, biocompatibility and low-costs of this approach and has stimulated its therapeutic use in many medical fields including;

orthopedics, sports medicine, dentistry, ENT, neurosurgery, ophthalmology, urology, and wound healing; as well as cosmetic, cardiothoracic, and maxillofacial surgery.

Scientific research and technology has provided new insight in understanding the biological potential of platelet in wound healing process.[20-22] Platelet rich plasma (PRP) preparations have been used both in surgical and outpatient procedures in the treatment of several muscoloskeletal problem with effective results.[20,21] PRP is increasingly used in treatment of chronic non-healing tendon injuries including the elbow, patella, and the achilles among others. The application of platelet rich plasma during arthroscopic rotator cuff repair is safe and effective, and produces results which seem to be stable with time.[23] Other orthopaedic applications include diabetic wound management, treatment of non-unions, and use in acute tendon injuries and plantar fasciitis.[24,25] Mishra et al suggested in their study that PRP treatment given to elbow epicondylar tendinosis patients prior to surgery can prevent the necessity to undergo the surgical procedure.[24] Other studies reported clinical efficacy of PRP applications in soft tissue surgical and conservative treatments.[20,24,26] There is mixed literature and controversy surrounding the efficacy of platelet gel to supplement autologous bone graft during instrumented posterolateral spinal fusion.[27-29]The potential efficacy of PRP to facilitate osteoinduction in spine fusion remains uncertain at present time.

Furthermore, PRP combined with proper nutrition (control of BMI), exercise and life-style, can act as a preventive agent in chronic and degenerative musculoskeletal disease.[30] Recent studies have documented the effectiveness of growth factors in chondrogenesis and preventing degeneration of the joints. Nakagawa et al, has reported the in vitro efficacy of autologous PRP in stimulating the proliferation and collagen synthesis of human chondrocytes, suggesting the use of this method in the treatment of cartilage defects.[31] Akeda et al successfully cultured porcine chondrocytes with PRP showing higher cell proliferation and proteoglycan and collagen synthesis.[32] In animal studies Frisbie et al reported clinical and

histologic improvement in osteoarthritis affected joints of horses after treatment with platelet rich plasma.[33] Moreover Wei et al in an experimental study done on animals showed the effectiveness of intrarticular injections of PRP with chondrocytes grown in vivo that resulted in the formation of new cartilage tissue.[34]

In clinical studies Anitua et al showed that an intra-articular injection of PRP could induce an increase in production of hyaluronic acid structure and promote angiogenesis and cell proliferation.[35] Cugat et al used platelet-rich growth factors (PRGF) to treat chondral defect in athletes and obtained good results, according to their experiences for other connective tissue repair, they showed that PRGF in physiological concentration is effective for the recovery of connective tissue furthermore local treatment is safe and does not alter the systemic concentrations of these proteins.[36] However which growth factors are more beneficial should be better understood. The complexity of interactions between different growth factors and the anabolic versus catabolic in vivo balance needs more evidence and scientific studies. Furthermore, Martinez et al, in a recent search of electronical database, noted there are also little data about PRP safety.[37] They also observed several methodologic limitations and, consequently, future research should focus on strong and well-designed RCTs that assess the efficacy and safety of PRP.

Kon et al have studied a group of 30 patients with symptomatic degenerative disease of the knee joints treated with three PRP intra-articular injections weekly; the follow up at 6 months showed positive effects on the function and symptoms with an improvement of 85% in scores evaluated for patients with median age less than 60 years, while in patients with age greater than 60 years, the improvement shown was only 30%.[38] Same authors recently presented their comparative study between HA and PRP: 91 patients with a mean age of 50.1 years with degenerative lesions and OA were followed up after injection of HA or PRP. Results were better in PRP group in clinical knee scores and pain score.[39]

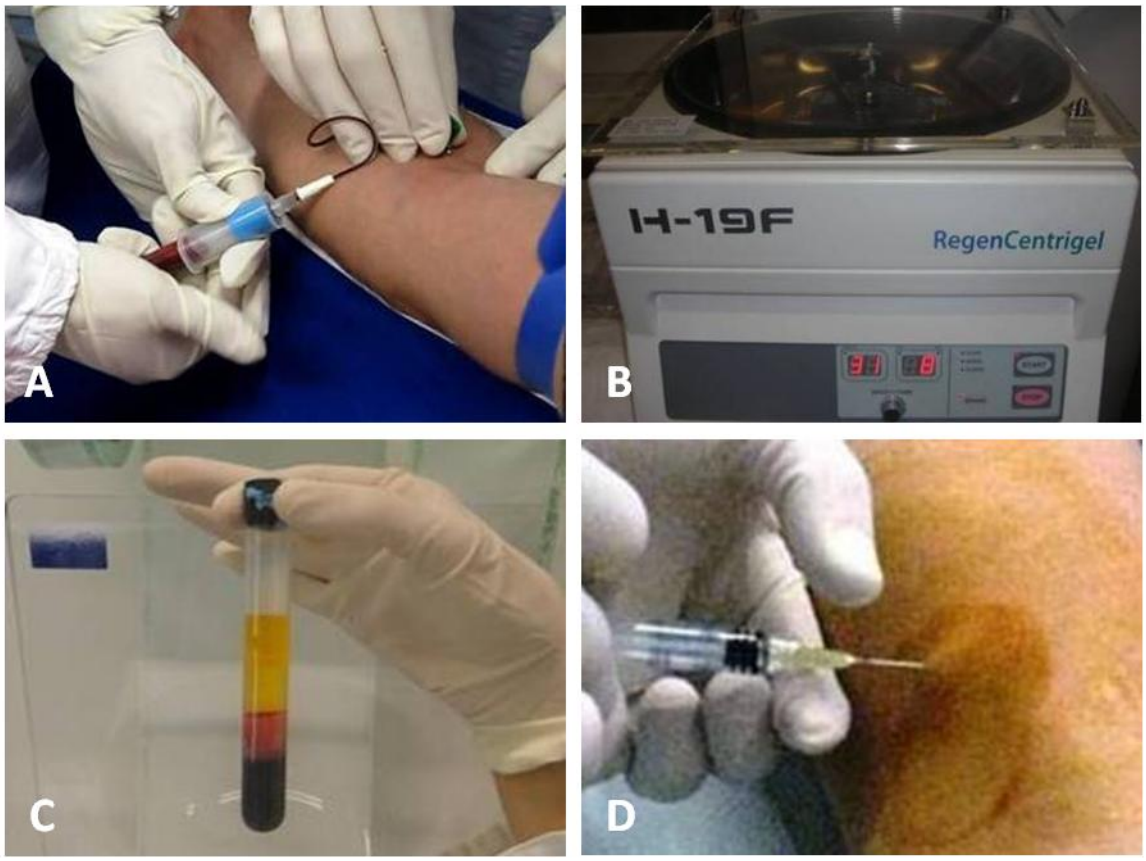
Finally several authors reported the use of growth factors and PRP preparations to stimulate mesenchymal stem cells (MSC) proliferation for chondrogenesis. Drengk et al reported in their in vitro study that platelet rich plasma has proliferative effects on autologous MSC and chondrocytes, suggesting advantages for one-step surgical procedure in cartilage transplantation using a combination of cells and gowth factors.[40] Mishra et al concluded in their study that the PRP enhances MSC proliferation and suggest that PRP causes chondrogenic differentiation of MSC in vitro.[41] These results were also evident in an in vivo study done by Milano et al that showed a more effective cartilage repair after microfracture associated to hydrogel scaffold with PRP.[42] Nishimoto et al suggested that simultaneous concentration of PRP and bone marrow cells (BMC), acting as a sources of growth factors and "working cells", could play important roles in future regenerative medicine.[43] This was supported by several authors stating that growth factors could act like as a carrier to fix chondrocytes into cartilage defects and can be combined with mesenchymal stem cells.[34,44] Buda et al reported the results of a group of patients treated with BMC and PRP at a same time in a collagen powder scaffold for grade 3 and 4 chondral lesion of the talus: at a mean follow up of 10 months AOFAS score improved compared to pre-op and 87.5% of patients were able to resume sport activity without complications.[45]

Preliminary data are encouraging, however further studies on clinical efficacy will clarify if simultaneous use of PRP and MSC could represents a real solution for regenerative medicine in cartilage repair.

Our Experience with PRP [46,47]

We used L-PRP according to Dohan Ehrenfest et al classification, in treating early arthritis of knee in 80 patients. The patients were treated with 2 intra-articular injections (1 month between each injection) of autologous PRGF (RegenLab-PRP®) by a supra-patellar approach.(figure 1) After the extraction of the blood, the sample got centrifuged for 9 min

and we obtained the fraction of PRGF and finally, we proceeded to the intrarticular infiltration. We used locally cold spray prior to the injections. After the infiltration, patient was allowed immediate weight bearing but was recommended functional rest and application of local ice 20 minutes every 2-3 hours during the day of treatment. There was also a period of abstinence from forceful efforts of the knee for at least 48 hours. We collected pain visual analogue scale (VAS) and Knee Osteoarthritis Outcome Score (KOOS) KOOS, VAS, Tegner, IKDC and MARX scores from pre-treatment to 6 and12 months at pre-treatment and 6-12 months post treatment; preliminary results are encouraging showing a trend towards improvement in both scores.



A. Aspiration, B. Centrifugation, C. PRP, D. Injection

Summary

PRP represents now a whole world of therapeutic applications with exciting and promising preliminary clinical results. However we believe that a standardization is warranted in terms of system of production, PRP characteristics, clinical indications, way of administration and therapeutic protocols. Moreover studies are currently under way to clarify some of the questions that still remain unanswered regarding the long-term durability of these procedures and the possible modifications that can still be done to achieve better results.

Bio-technology is progressing at a rapid pace, exploring new horizons and allowing the introduction of numerous products for clinical application. However, carefully conducted randomised prospective studies for each of these innovations should be carried out to validate the safety and efficacy. The use of autologous growth factors in the form of PRP may be just the beginning of a new medical frontier known as ‘‘orthobiologics.’’

Dr. Vivek Mahajan is working as an assistant professor in the department of orthopaedics in Father Muller Medical College, Mangalore. He has published extensively on treatment of cartilage repair in international peer-reviewed journals. He has done a fellowship in cartilage repair in Milan, Italy with Dr. Alberto Gobbi who was the Scientific Program Chair of the recent World Cartilage Meeting in the US and has been on the Board of the International Cartilage Repair Society for several years.

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