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PRP in Knee Osteoarthritis- Current review

Sandeep Patel[1], Vishal Kumar[1], Shivam Rai[1]

Abstract

In the past decade various researchers have demonstrated positive results of PRP for use in symptomatic treatment of OA with good pain relief and improved function. The clinical results are attributed to its anti-inflammatory effects. The preclinical data is abundant and demonstrates the multiple positive effects of PRP in joint homeostasis including chondral remodeling. The release of growth factors from PRP occurs immediately and lasts for around three weeks and the clinical effect tends to wane down by the end of the year. Prolonged and sustained release of growth factors from platelets could possibly help in much better biological healing and sustained clinical effects. The purpose of this narrative review is to discuss the available relevant evidence that supports the clinical use of PRP in osteoarthritis, highlighting those variables we perceive as critical. The efficacy of PRP is of much interest to musculoskeletal specialists because of its disease modifying and regenerative capability, compared with conventional injection regimen.

Keywords: platelet rich plasma, Osteoarthritis

Introduction

Osteoarthritis (OA) is a common disease that will affect almost half the population at some point in their lives and is a cause of pain and decreased functional capacity. OA is characterized by progressive destruction of joint cartilage and changes in synovial environment and joint homeostasis(1). New nonoperative options are being proposed to treat earlier stages of joint degeneration to provide symptomatic relief and delay surgical intervention

Over the last 10 years there has been a trend of using growth factors for tissue repair and maintenance of normal tissue structure. Platelet-rich plasma (PRP) is the frontrunner and is evolving into a promising solution for a number of Orthopaedics conditions like osteoarthritis, tendinopathies and nonunion. PRP therapy is becoming popular as it is easy to prepare, safe and well tolerated. Its popularity is also due to some famous elite athletes and celebrities opting for the treatment.

In 1998, platelet concentrates came to be known as platelet-rich plasma (PRP), generally defined as a "volume of autologous plasma containing a higher platelet count than peripheral blood (150,000–350,000 platelets/μl)"(2). Thereafter multiple systems have been developed to concentrate platelets and remove erythrocytes (RBCs) and, in some cases, also leukocytes (WBCs. For the purpose of this review, PRP or PRP products refer to any product derived from a platelet concentrate (PC), optionally containing WBCs, from whole blood.

A number of randomized trials have reported favorable outcome of PRP and several systemic reviews and meta-analysis have noted that PRP is safe and effective orthobiologic in treatment of knee OA compared to other non operative modalities.

Mechanism of action of PRP

PRP has 7 fundamental proteins: platelet derived growth factors (PDGF), transforming growth factor–β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and adhesive proteins – fibrin, fibronectin, and vitronectin(2).

The pathogenesis of OA is primarily because of the alteration of normal metabolism within joint, which favors increased catabolism and decreased anabolism.PRP aids in balancing this process of anabolism and catabolism. PRP appears to aid in biological process of healing by providing the pool of growth factors within alfa granules of platelets. Platelet alfa-granules contain and release numerous growth factors and it is the cocktail of growth factors which is helpful for responsible for creating a positive balance within joint(3). The overall effects of PRP within joint is depicted in fig 1.

They overall act at joint homeostasis by acting on cartilage by decreasing catabolism, increasing anabolism and promoting chondral remodeling. PRP is also known to improve the cartilage layer by increasing Collagen II and proteoglycans which forms the matrix of cartilage(4). PRP also has a positive role on the chondrocytes where it has shown its positive role on chondrocyte proliferation and inhibition of chondrocyte apoptosis through complex pathways (5).

Through cell membrane adherence, aggregation, clot formation, and release of substances, PRP influence the reactivity of blood vessels and blood cell types involved in angiogenesis and inflammation. Over the last decade, the vast anti-inflammatory potential of PRP is being more and more recognized and is being attributed for the positive clinical results. An overall decrease in the joint inflammation is due to the regulation of various pathways (5–7).

Platelets also store antibacterial and fungicidal proteins, metalloproteases, coagulation factors, and membrane glycoproteins, which may influence

[1]Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address of Correspondence:
Dr Sandeep Patel
MBBS, MS Ortho, DNB
Postgraduate Institute of Medical Education and Research, Chandigarh, India
Email- sandeepdrpatelortho@gmail.com


Dr. Sandeep Patel


Dr. Vishal Kumar


Dr. Shivam Rai

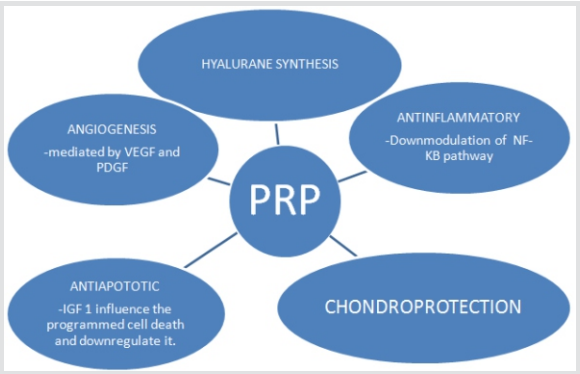

Figure 1: various effects of PRP which brings a positive change in knee OA.

inflammation by inducing the synthesis of other integrins, interleukins, and chemokines. Dense granules in platelets store and release ADP, ATP, calcium ions, histamine, serotonin, and dopamine, which are active in tissue modulation and regeneration. Platelet degranulation begins within 10 minutes of exposure to clotting cascade factors (such as thrombin) or, in their absence, contact to exposed basement membrane. The majority of GF secretion occurs within the first hour, although continued release occurs throughout the period of platelet viability (7 days).

Both in vitro and animal studies clearly demonstrate that PRP has positive influence on knee OA by its chondral remodeling and anti-inflammatorypotential. The authors in their previous study(8) in Dunkin Harley pig have demonstrated both the effects, but the more clinically relevant and important effects are attributed to anti-inflammatoty effects. In the clinical scenario, we feel that it is the anti-inflammatoryeffectwhich is responsible for the positive results(8).

Preparation of PRP

PRP is the plasma fraction of autologous blood with platelet concentration above baseline. Platelet counts of 4–5 times of the baseline (1.5–4.5 × 105/μL) is required to label the product as PRP. Methodology to prepare PRP and its derived products differs widely. Briefly, they rely upon single centrifugation, double centrifugation, or blood selective filtration procedures, and on manual or automatic systems operated in open or closed circuits. And at least 25–30 ready-to-use kits are commercially available.

Due to their complex composition and to inter- and intra-individual differences(9), each PRP is unique and very difficult, if not impossible, to characterize. As a result,a set of critical variables are used to define PRP and a detailed description of the preparation protocol. These variables usually include (1) the proportion of platelets in PRP to platelets in whole blood (platelet enrichment factor, PEF), (2) presence/absence of WBCs, and (3) method of activation.

The number of spins (single versus double), centrifugal forces and time, use of WBC Filter, type of Preparation (Buffy coat based versus Plasma Based versus platelet pellet based techniques) all alter the PRP product in terms of platelet count and leucocyte concentration. Based on the variability in yield, it became necessary to classify PRP. Mishra and colleagues(10) proposed to classify PRPs with three parameters: first two parameters used were increased WBC and use of activator based on which the'type' of PRP was: (a) increased WBCs and no activation; (b) increased WBCs and activated; (c) minimal/no WBCs and no activation; (d) minimal/no WBCs and activated. The third parameter was its platelet enrichment factor, A if the PRP contains a platelet concentration at or above five times the baseline, or B if platelet concentration is less than five times the baseline. The PAW (Platelets, Activation, White cells) classification system(11)also includes the same three variables: (1) the absolute platelet concentration (P); (2) the method of activation (A); (3) the presence or absence of WBCs and neutrophils (W) relative to the baseline; but is a more elaborate classification. Platelets are categorized as P1 (baseline) to P4 (>1.2 million platelets/μl), activation as either exogenous (X) or not, and WBCs and neutrophils as either above or below baseline. Mautner and colleagues(12) advocated for reporting at least platelet concentration (cells/μl, volume injected), leukocyte concentration, including the concentration of neutrophils (if >1%), RBC concentration and activation by exogenous agents. More recently, the DEPA (Dose of injected platelets, Efficiency of production, Purity of the PRP, Activation of the PRP) classification system(13) was proposed. This system takes into account (1) the dose of injected platelets from A (>5 billion) to D (<1 billion); (2) platelet capture efficiency from blood from A (>90%) to D (<30%); (3) the % platelets compared with RBCs and leukocytes in the PRP from A (>90%, very pure) to D (<30%, whole blood PRP); and, (4) the activation process. Thus, an 'AAA' DEPA score refers to an injection of PRP with a very high dose of platelets (>5 billion) with little contamination from RBCs and with very high platelet recovery efficiency from blood. However, none of these methods has been formally adopted and PRP descriptions are still very heterogeneous.

Activation of platelets

The term "activation" refers to 2 key processes that are initiated during PRP preparation: (1) degranulation of platelets to release GFs from α-granules and (2) fibrinogen cleavage to initiate matrix formation, a clotting process which allows the formation of a platelet gel, and therefore to confine the secretion of molecules to the chosen site. It can be done by using 10%CaCl2 ,10%autologous thrombin or mixture of 10%CaCl2 +10% autologous thrombin. Since GFs are very potent molecules even small increase in levels will impart significant effect. Use of these activators led to an increase in level of GFs that was immediate and was sustained upto 24 hrs(14). Platelet concentration, fibrinogen concentration and the enzymes involved in procoagulant pathway influence the final fibrin content. The above factors regulate the duration of GF release at the injection site.

Platelet activation can be broadly achieved by two ways- Exogenous activation and Endogenous Activation. Exogenous activation is by using PRP with Bovine or autologous thrombin, 10% CaCl2 or combination. Calcium chloride is the most common activator used in the majority of clinical studies. The other type of activation is endogenous activation and it happens when Platelets come in contact with tissue inside the joint. The proponents of using PRP without exogenous activator rely on endogenous activation(15–17).

Cavallo et. al (18) have compared the amount of growth factor released when PRP was used with activator and when PRP was used alone and concluded that there is increase in amount of GFs release when PRP was used with activator and the effect was immediate and sustained for 24 hrs.

Multiple studies have been conducted for PRP in OA knee and many of them have used activators (like calcium chloride, Photoactivation, freezing) and many of them haven't used activator; but as of now there are no conclusive study comparing directly the outcome of using PRP along with activator vs PRP alone.

Which PRP: Leucocyte rich PRP (LR-PRP) Versus Leucocyte Poor PRP (LP PRP)

Leucocyte rich PRP(LR-PRP) and leucocyte poor PRP(LP-PRP) both have been used by various authors for OA knee. Initially there were concerns regarding the presence of leucocytes in PRP as they have pro inflammatory mediators like MMP-2, MMP-3, MMP-9 which could be deleterious(19). Significant cell death and pro inflammatory mediator production was noted by Braun et al.(20)in synovial cells treated with LR-PRP and RBCs in comparison to LP-PRP. Sanchez et al(21) and Patel et al(22)used LP-PRP whereas Filardo et al(23) used LR-PRP among the initial studies. However Filardo et al.(23)in later clinical trials compared both LR-PRP and LP-PRP and noted both to equally efficacious but noted more transient adverse events following injections in LR-PRP arm. Riboh et al(24). in their meta-analysis which included 6 RCTs and 3 prospective comparative studies (total of 1055 patients), noted that injections of LP-PRP had resulted in significantly better WOMAC scores compared to HA treatment arm. No such difference was observed with LR-PRP. They have also concluded that LP-PRP was the highest ranked treatment modality in terms of both clinical efficacy (IKDC and WOMAC). The current literature supports the use of both LP-PRP and LR- PRP for OA knee, but leucocyte-poor PRP appears to be better than leucocyte-rich PRP for OA Knee as it has less adverse effects. It is to be noted that in lateral epicondylitis, however LR PRP is shown to be better than LP PRP as shown in recent multicentric trial (25).

Clinical studies

In this review we have gone through multiple clinical trials and meta-analysis conducted over the past ten years and researchers have shown growing interest in exploring PRP as a novel treatment option in treatment of early osteoarthritis knee. There has been an increasing trend in use of PRP and it is reflected by the increasing number of publications. In most of the studies we have have found the supremacy of PRP in alleviating pain and improving knee score over other intra articular injections.

Multiple RCTs(21,22) and meta-analysis(26–28)have established the safety of PRP over other intraarticular option. Sanchez et al(21) were the first to establish the safety of autologous PRP for intra-articular usage. Patel et al(22)in their study also documented the safety of autologous PRP for intra articular injections. 3 meta-analysis(26–28) evaluated adverse events of PRP versus HA or placebo in knee osteoarthritis and concluded that no severe complications were recorded and all adverse events were self resolving in days. All these articles suggested no statistical difference in adverse events between PRP vs HA or placebo. Most of the recent meta-analysis concludes that pooled relative risk for adverse events following PRP injection is comparable to HA administration indicating no difference between the regimens in terms of adverse effects.

Several studies have documented superior efficacy of PRP over placebo in the treatment of knee osteoarthritis. Patel et al.(22)in their randomized clinical trial were the first to establish the supremacy of PRP over placebo both in terms of effectiveness (significantly better WOMAC scores in PRP group). They noticed benefits as early as 3 weeks and the effect was sustained at their last follow up of 6 months. Smith et al(29)in their US FDA sanctioned, Randomized, double blind, placebo controlled trial noted an improvement of 78% from baseline scores in PRP group versus 7% in placebo group.

Efficacy of PRP has been compared with HA in multiple RCTs(4,16,30,31), prospective studies(15,32), and meta-analysis and most of them have labeled the supremacy of PRP over HA in terms of pain relief and functional score at 3, 6, 12 months. Kon et al.(33)in their trial of 150 patients which had 3 groups of 50 each(Group A- Three PRP injections, Group B-HMW-HA, Group C-LMW-HA); established good outcomes in IKDC scores in those treated with intraarticular PRP injections in patients with early degenerative OA. They also quoted better results were observed in those who were younger and with lower BMI. Spakova et al.(15) treated 120 patients with grade 1, 2, 3 KL and compared the efficacy of 3 PRP injections versus 3 HA injections and measured the outcome in terms of WOMAC and pain intensity scale and established that the better improvement in scores were recorded at 3 and 6 months follow up in group which received PRP. Cole et al.(34) in their similar study compared efficacy of PRP over HA and concluded similar improvement in primary outcome measure (patient reported WOMAC pain score), but had significant improvement in other patient related parameters like improvement in inflammatory marker levels which suggested better efficacy of PRP over HA. On the other hand, studies by Duymus et al(16) and Filardo et al(23) mentions PRP to be similar to Viscosupplementation, however a clear outlook on the papers demonstrate that scores were better with PRP but not significant (35) and at 12 months the results were better in PRP group(16). It is to be noted that there is not a single study till date which states the other way round that viscosupplements to be superior over PRP.

Multiple meta-analysisalso favors the use of PRP over other intra articular injections. Meta-analysis by Chang et al(36), Laudy et al.(37), Shen et al.(28)all showed a statistically significant clinical improvement in favor of PRP injection in terms of pain improvement on VAS scale and improvement in WOMAC score. Meta-analysis by Dai et al(26) concluded that similar improvements from baseline scores were recorded in both PRP and HA arms at 6 months duration but PRP seemed to have better results at 12 months of follow up.

The right dosage of PRP has been very confusing as there are varying dosage schedule in literature ranging from single injection to 2 injections, to multiple injections with varying intervals between injections (weekly interval, 2 weekly interval, 3 weekly interval etc). Initial studies used three injection regimen at three weekly intervals as they used HA as a standard to compare. Patel et al.(22)were the first to compare two dosage schedule (single versus double injection) where they did not notice any difference between single injection and double injections and concluded that single injection is as better as double injection. Small sample size in their study could be a potential limitation as that could not have picked small differences. Kavadar et al(38) compared 3 groups of patients who received single injection, two injections and three injections respectively and noted positive results in terms of pain and functional results in moderate OA in all groups but concluded by recommending a minimum of atleast two injections for better results. Gormeli et al.(30)also compared three doses PRP regimen with single dose regimen of PRP, HA and placebo. They also concluded 3 injection regimen of PRP to be better than single injection in achieving statistically significant clinical outcome in early knee OA.

Chouhan et al(39)recently in their study on guinea pig noted better anti inflammatory effect of 3 doses of PRP compared to a single dose PRP at 6 months follow up on histopathological examination. There was no difference at 3 months.

Majority of the studies done previously included early OA knee and they have consistently shown better outcome in terms of symptomatic improvement. Kon et al(33) and Hassan et al(40) in their studies have compared the effectiveness of PRP in early versus late OA and have found statistically better clinical outcome in early OA where as the role of PRP in advancedOA is quite a grey zone.

There are latest developments where in combination of HA and PRP are being tried and proven to be effective(31). Preclinical studies of combination of PRP with biomaterials is also emerging to improve PRP potency. Intraosseous PRP into subchondral bone of tibial and femoral condyles along with intra articular PRP has been introduced by Sanchez et al(41).for advanced stage OA where they demonstrated superior results over only intraarticular PRP.

PEARLS OF WISDOM
• Platelet-rich-plasma (PRP) is one of the several "cellular therapies" available for the conservative treatment of knee osteoarthrosiswhich has proven to be safe.
• PRP exerts its effects by anti-inflammatory, anti-apototic, chondroprotective and angiogenic pathways mediated by direct and indirect pathways.
• Like most other such therapies, there is no standardization of the technique of preparation, timing or frequency of injections. The makes comparison of data on outcomes very difficult to analyze.
• Patients with early OA and low body mass index are suitable candidates for intra-articular injection(s) of PRP.
• The use of PRP in combination with hyaluronic acid injections or as subchondral injections or with other cellular modalities are potential future tools for treatment of knee OA.

Conclusions

Results from RCT's and meta-analysis suggest PRP to be a safe and effective therapy for symptomatic relief at short and medium term (6-12 months) in OA Knee. The ideal patients are Early stage OA (KL stage 1,2) with low BMI. Both Leucocyte rich and Leucocyte Poor PRP are effective but LP PRP has fewer pain and swelling adverse effects. Both single and multiple doses of PRP are effective for OA Knee but multiple injections seem better.

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