Review Article

# Orthobiologics and platelet rich plasma

*Mandeep S Dhillon, Prateek Behera, Sandeep Patel, Vijay Shetty*[1]

## Abstract

Orthobiologics have evolved to the extent that they significantly influence modern orthopedic surgical practice. A better understanding of the role of various growth factors and cells in the process of tendon healing, ligament repair, cartilage regeneration and bone formation has stimulated focused research in many chronic musculoskeletal ailments. Investigators have published results of laboratory as well as clinical studies, using orthobiologics like platelet rich plasma, stem cells, autologous conditioned serum etc., with variable results. However, a clear consensus over the best orthobiologic substance and the method of preparation and usage of these substances is lacking. Much of the confusion is due to the fact that studies ranging from RCTs to case reports present variable results, and the interpretations are wide-ranging. We have reviewed the available orthobiologics related data with a focus on platelet rich plasma in orthopedic conditions.

**Key words:** Platelet rich plasma, orthobiologics, tendon healing, ligament repair

## Introduction

Sports related injuries among professional and recreational athletes are increasingly encountered and diagnosed and demand a quick return to preinjury level of sporting activities.[1] "Orthobiologics", refers to the use of biological substances to help musculoskeletal injuries heal quicker. They are used to improve the healing of fractured bones and injured muscles, tendons and ligaments and are derived from substances that are naturally found in body.[2] When they are used in concentrations many times the normal, they can potentially help speed up the healing processes.[2]

The substances include bone grafts, autologous blood, platelet-rich plasma (PRP), autologous conditioned serum and stem cells.[2] Bone grafts act by their osteoinductive, osteoconductive and osteogenic properties to stimulate new bone formation and have no effect on the healing of muscles, tendons and ligaments.[3] On the other hand, autologous blood, PRP and autologous conditioned serum deliver growth factors to the diseased areas to stimulate the repair process.[4-6] Stem cells are unique in the sense that they provide a means to replenish the dead or dying cells in areas where the cells have limited regenerative capabilities.[7] Each of these biologic substances has some advantages and disadvantages, which would be further elaborated in this article.

## Rationale for Orthobiologic Substance use

Though the bones and joints make up the basic skeletal framework of the body, the musculo-tendinous units are the prime mediators of movement. While the muscle cells have adequate blood supply, they lack the ability to regenerate after injury; on the other hand, tendons are precariously supplied by blood vessels, hence injuries to the musculo-tendinous areas are notorious for inadequate healing and chronicity.[8,9]

Injuries to the musculo tendinous structures may be acute or chronic, with the chronic conditions being more problematic. These chronic conditions are believed to be a result of overuse, which occurs as a result of multiple micro-traumatic events that cause disruption of the internal structure of the tendon and degeneration of the cells and matrix. This fails to mature into normal tendon and at times, such injuries result in tendinosis,[8] which is often accompanied by what is called as an angiofibroblastic degeneration.[9] This type of injury is seen in lateral epicondylar tendinopathy, rotator cuff injuries, patellar tendinopathy, Achilles tendinopathy and plantar fasciitis; consequently most of the research in the field of orthobiologics is being done in these areas.[4]

Department of Orthopaedics, PGIMER, Chandigarh, India, [1]Hiranandani Hospital, Povai, Mumbai

**Address for correspondence:** Dr. Mandeep S. Dhillon, Professor, Department of Orthopaedics, PGIMER, Chandigarh, India. E-mail: drdhillon@gmail.com

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Additionally, the orthobiologics are now being explored in early osteoarthritis of knee,[10] cruciate ligament injuries and fracture nonunions.[3,6]

## Orthobiologic Options

The concept of employing growth factors for healing of musculoskeletal lesions is relatively recent. Researchers have shifted focus from recombinant growth factors (considering the high cost, short life span, inefficient delivery system and the requirement of high doses for achieving therapeutic effects) to autologous blood products.[6] Historically, autogenous fibrin gel was initially described in 1990.[11] PRP was used for the first time in bone repair by Marx *et al*.,[12] (1998) who published a case series of 88 patients having mandibular continuity defect and were treated with bone grafting. In half of these patients they had added PRP to the graft and these showed an increase in maturity and consolidation of graft in subsequent radiographs.

Autologous blood injection (ABI) is the simplest method of delivering blood derived growth factors. The procedure includes drawing of venous blood from the patient and then injecting it at the desired area. Although this delivers growth factors contained in platelets, red and white blood cells are also delivered, which have no healing properties. Consequently, the results of ABI have been variable. Edwards *et al*.,[13] Connell *et al*.,[14] Ozturan *et al*.,[15] Creaney *et al*.,[16] and Thanasas *et al*.[17] have reported good results with ABI in lateral epicondylitis, while Kazemi *et al*.[18] found no benefit of ABI over corticosteroids. On the other hand, Suresh *et al*.[19] used ABI for refractory medial epicondylitis and reported encouraging results. James *et al*.[20] reported a significant improvement in VISA (Victorian Institute of Sport Assessment) score with ABI in patellar tendinopathy.

The consideration that growth factors are primarily contained in the alpha granules of the platelet has led to researcher focus being directed towards more effective use of these factors and hence the growth factor delivery system graduated from the use of autologous whole blood to the use of concentrated platelets in the form of PRP. A pubmed search conducted on 13th April 2013 with the keywords "Platelet rich plasma" revealed 6400 results while a similar search that had been done on 16th November 2011 had returned 5928 results— a total 637 articles were added in just 18 months.

Autologous conditioned serum (ACS) has also been researched for its application in orthopaedic conditions. It is prepared by incubation of 50 ml venous blood for 24 h in 5% $CO_2$. Incubation of blood is carried out with small glass beads, which need to be specially processed to make their pH similar to distilled water. Following incubation, centrifugation is done to obtain the ACS.[5,21] Preparation process leads to an accumulation of interleukin-1 receptor antagonist and several growth factors, including insulin-like growth factor-1, platelet-derived growth factor and transforming growth factor-β1, in the liquid blood phase. ACS has been used in human trials by Becker *et al*.,[21] for treatment of lumbar radiculopathy while Moser *et al*.[22] have used it for knee osteoarthritis. Human studies are limited and cannot be sufficiently evaluated to provide any recommendation for the use of ACS at present. Additionally, the preparation procedure is cumbersome and the requirements of special glass beads, laminar air flow system and incubation systems make it a relatively unattractive option.

Stem cells are of two basic types – Embryonic stem cells which are found in the early developmental phase of an individual and mesenchymal stem cells which are found in adults. Mesenchymal stem cells (MSCs) are considered to be an orthobiologic substance. A cell can be called a stem cell if it has the capacity to differentiate into multiple types of cells and the cell is able to self-renew.[7] The ability of a stem cell to simultaneously maintain the stem cell pool and generate daughter cells which can terminally differentiate into specialized tissues is the unique capability of such cells. Mesenchymal stem cells can differentiate towards cartilage, tendon and bone cells. They can be isolated from a number of mesenchymal tissues like bone marrow, fat, synovial membrane, periosteum and others. A common source of MSCs is the bone marrow, especially from the iliac crest. The iliac crests are subcutaneous and are easily palpable, thus making the stem cells harvesting process easy. Bone marrow is aspirated from the region of posterior superior iliac spine and the MSCs contained are used either by concentrating the aspirate so as to use the natively available stem cells[23] or the cells are separated and cultured[24] in laboratory media to increase their numbers before being used. Stem cells have been used with encouraging results in treatment of nonunions, osteonecrosis of femoral head, spinal fusion enhancement and for filling of bone defects and voids.[7] In tendon injuries the application of stem cell is presently limited to experimental animal models with no clinical studies available. In view of the fact that the preparation techniques are difficult and resource demanding, along with a relative lack of clinical studies supporting the use of stem cells in various musculoskeletal lesions, a recommendation for the routine use of stem cells cannot be made as yet.

## Platelet rich Plasma: Classification and types

PRP is the plasma fraction of autologous blood which has a platelet concentration above baseline. Other names

by which PRP has been known include platelet-enriched plasma (PeRP), platelet-rich concentrate (PRC) and autogenous platelet gel.[6] The normal platelet count in whole blood in a healthy individual is between 1.5-4.5 × $10^5$/μL. To be labeled as PRP, a platelet count of 4-5 times of the baseline should be present in the platelet concentrate.

Platelets are formed from megakaryocytes in the marrow. Platelets contain granules namely α, δ and λ. α granules play a pivotal role in platelet function. There are approximately 50 to 80 α granules per formed platelet[25] and contain more than 30 proteins including platelet-derived growth factor (PDGF), transforming growth factor (TGF-β, β1 and β2 isomers), platelet factor 4 (PF4), interleukin-1 (IL-1), platelet-derived angiogenesis factor (PDAF), VEGF, epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF) etc., The properties of PRP are based on the production and release of these factors when the platelets are activated. Platelets begin secreting these proteins within 10 minutes of clotting. After initial release of growth factors, the platelets synthesize and secrete additional such factors for the remaining days of their life span.[6]

Preparation of PRP includes drawing of blood into a bag or a tube containing an anticoagulant (CPDA) followed by centrifugation to separate the red cells from the rest of the blood components. Separation of the platelets from the red cells and the platelet poor plasma leads to retrieval of PRP. This PRP can now be directly used as leukocyte-rich PRP or it may be passed through a leukocyte filter to obtain leukocyte poor PRP. PRP application may be done in two ways – nonactivated and activated. While the activation process consists of simultaneous application of calcium chloride to activate the PRP, the nonactivated application depends on the activation of platelets after coming in contact with collagen of the tissues. For surgical applications, PRP is often treated with calcium chloride before application of thrombin, which forms a gel-like substance for direct application.[26]

Previously reported studies have used the PRP in either of the two forms leukocyte-rich or leukocyte poor PRP, as the exact influence of leukocytes on the local injection site was not clearly known. Moreover, lack of standardization of the type of PRP used tended to make comparison between studies difficult and unreliable. Mishra *et al*.[27] have proposed the Sports Medicine Platelet-Rich Plasma classification system [Table 1]. This system takes into consideration the platelet count, the activation method and the leukocyte count to divide PRP into four types, with each having two further subtypes.

Some recent studies in the literature strongly support the notion that leukocyte poor PRP is better than leukocyte-rich PRP.[28,29] The platelet concentration process also leads to a simultaneous concentration of leukocytes. While previous studies only speculated that increased residual leukocytes could produce localized inflammation and hence prolonged early postinjection pain,[17] studies by Dragoo *et al*.[28] and Mc Carrel *et al*.[29] have conclusively demonstrated significant inflammatory capabilities of leukocyte-rich PRP. Thus, the use of leukocyte-poor PRP may be considered better as just by separating the leukocytes, one may be able to provide better pain relief to the patients. On the other hand, almost all studies published till now have reported no adverse effects by use of PRP in any form.

## Applications of Platelet-rich Plasma in Musculoskeletal Problems

PRP has been used in diverse musculoskeletal conditions like lateral epicondylar tendinopathy, rotator cuff tears, sub-acromial impingement, shoulder osteoarthritis, patellar tendinosis, osteoarthritis of the knee, tendo-achilles tears, ACL reconstruction, plantar fasciitis, nonunion of bones and topically to control bleeding after knee arthroplasty.[30] Considering that there are numerous conditions where PRP is being used, both in clinical or in laboratory settings, it often becomes difficult to get the appropriate evidence for the usage of PRP. In this review, we undertook a focused pubmed based review, with PRP being the common key word and other keywords relevant to the particular orthopedic condition in question [Table 2]. We then segregated the studies into randomized control trials (RCTs), cohort studies and others. Of all the available publications, we attempted to focus on level 1 and level 2 studies only, with significant numbers of patients. For this review, we have focused only on five areas of orthopedic use, i.e. lateral epicondylar tendinopathy, rotator cuff tear, patellar tendinosis, osteoarthritis of the knee and Achilles tendinopathy, as these are the commonest areas for chronicity and confusion regarding orthobiologic interventions.

## Lateral Epicondylar Tendinopathy

Though lateral epicondylar tendinopathy can potentially

**Table 1: Sports medicine platelet rich plasma classification system**

| Type | White blood cells | Activation of PRP | Concentration of platelets |
|---|---|---|---|
| 1 | Increased | No activation | A,5× or >B,<5× |
| 2 | Increased | Activated | A,5× or >B,<5× |
| 3 | Minimal or absent | No activation | A,5× or >B,<5× |
| 4 | Minimal or absent | Activated | A,5× or >B,<5× |

(Adapted from Mishra *et al*.[27]). PRP=Platelet-rich plasma

be treated well with conventional established protocols, a significant number of patients do become resistant; these are the patients who could potentially have significant benefit from PRP. Mishra and Pavelko[31] were the first to use PRP injection for resistant lateral epicondylitis and reported good results in terms of pain relief and functional improvement in their pilot study. Peerbooms *et al*.[32] conducted a RCT with 100 patients, 51 of whom received PRP injection and 49 received corticosteroid injections and reported better improvement with PRP over a period of 1 year. Gosens *et al*.[33] followed up these patients for the subsequent year and reported a sustained improvement with PRP use in comparison to corticosteroids. In the management of resistant lateral epicondylitis, PRP may be considered better than corticosteroid injections, which were considered for long as the gold standard. In an attempt to increase injection accuracy, Chaudhary *et al*.[34] used ultrasonographic guidance for injection and noted a trend toward an increase in the vascularity at the musculo-tendinous junction of the extensor tendons. Creaney *et al*.[16] reported similar improvements in pain and function scores with PRP and ABI, but noted a lesser rate of conversion to surgery among patients receiving PRP injections. Thanasas *et al*.[17] have also shown encouraging results for PRP use compared to ABI in resistant tennis elbow patients [Table 3].

From the available evidences one may offer a PRP injection instead of a corticosteroid injection to patients who have failed to obtain improvement with conservative methods and in whom a surgical treatment option is being considered.

**Table 2: Studies of PRP in orthopedic conditions as searched on pubmed**

| Keywords for pubmed search | Total hits | RCTs | Cohort studies | Other studies | Selected studies |
|---|---|---|---|---|---|
| Lateral epicondylar tendinopathy | | | | | |
| PRP | 28 | 3 | 1 | - | 4 |
| Tennis elbow | | | | | |
| Lateral epicondylar tendinopathy | | | | | |
| Rotator cuff injuries | | | | | |
| PRP | 47 | 6 | 1 | 1 case report | 4 |
| Rotator cuff tear | | | | | |
| Rotator cuff repair | | | | | |
| Knee osteoarthritis | | | | | |
| PRP | 47 | 4 | 2 | 1 pilot | 4 |
| Knee osteoarthritis | | | | | |
| Achilles tendinopathy | | | | | |
| PRP | 37 | 3 | 2 | 1 pilot | 6 |
| Achilles tendinopathy | | | | 1 case control | |
| Achilles tendon rupture | | | | | |
| Patellar tendinopathy | | | | | |
| PRP | 15 | 1 | 1 | 1 case control | 3 |
| Patellar tendinopathy | | | | | |
| Jumper's knee | | | | | |

RCTs = Randomized control trials, PRP = Platelet rich plasma

## Rotator Cuff Injuries

Rotator cuff tears tend to occur with two age peaks, i.e. in older patients and in younger patients involved in sports. In the older population, some degenerative changes are expected to be present alongside the tear and there are chances that a meticulously performed rotator cuff repair may fail or heal sub-optimally. It is important to note that the distal part of the rotator tendon has inherently poor healing capabilities; PRP with its growth factors may thus be an attractive option for the stimulation of the healing of this tendon. Many shoulder surgeons have started using PRP intraoperatively after performing rotator cuff repairs.[35-37]

Randelli *et al*.[35] were the first to conduct an uncontrolled pilot study of PRP augmentation along with arthroscopic rotator cuff repair. In their 14 patients injected with PRP activated with thrombin at the tendon footprint after repair, they reported statistically significant improvements in VAS, constant and UCLA shoulder scores compared

**Table 3: Summary of studies using PRP for resistant lateral epicondylitis**

| Authors | Study type | Patients studied | Controls | PRP type | USG guidance | Outcome measure | Followup | Results |
|---|---|---|---|---|---|---|---|---|
| Mishra and Pavelko[31] | Cohort study | 15 cases vs. 5 | Bupivacaine | 1A | No | VAS, Mayo elbow score | 4,8 weeks, 6 months | 81% reduction in pain in PRP group at 6 months |
| Peerbooms *et al*.[32] Gosens *et al*.[33] | RCT | 51 cases vs. 49 | Cortisone | 1A | No | VAS, DASH | 1 years | Improvement in VAS-PRP 53% *vs.* cortisone 24% at 6 months and 63% *vs.* 24% at 1 year |
| Creaney *et al*.[16] | Prospective randomised trial | 80 cases vs. 70 | Autologous blood | 1B | Yes | PRTEE | 1,3 and 6 months | Improvement in PRTEE at 6 months 35.8 in PRP and 46.8 in ABI group with higher conversion to surgery in ABI group |
| Thanasas *et al*.[17] | RCT | 14 cases vs. 14 | Autologous blood | 1A | No | VAS, Liverpool elbow score | 6 weeks, 3 and 6 months | 70.8% improvement in PRP group and 57.8% in the autologous blood group at 6 months |

RCTs = Randomized control trials, PRP = Platelet rich plasma, USG = Ultrasonogram, VAS = Visual analog scale, DASH = Disability of arm shoulder hand score, PRTEE = Patient related tennis elbow evaluation, ABI = Autologous blood injection

to preoperative values. They subsequently conducted a RCT[36] and reported that autologous PRP reduced pain in the first postoperative month and that the longterm results of subgroups of grade 1 and 2 tears suggested that PRP positively affected cuff healing. Rha *et al*.[37] compared ultrasound guided PRP injection with dry needling and concluded that autologous PRP injections lead to a progressive reduction in the pain and disability when compared to dry needling. However, not all studies have shown good results of the use of PRP; Weber *et al*.[38] in their prospective, randomized double blind study reported that platelet-rich fibrin matrix did not show significant improvement in perioperative morbidity, clinical outcomes, or structural integrity. Castricini *et al*.[39] concluded that their study did not support the use of autologous PRP rich fibrin matrix for augmentation of small or medium rotator cuff tear to augment healing [Table 4] summarizes the studies reporting PRP use in rotator cuff tear.

The evidences available so far do not provide a clear picture regarding the use of PRP in rotator cuff tears. However, PRP may be used in rotator cuff injuries either as an adjunct to surgery, or as stand alone injections after explaining the prognosis and the limited available evidences to the patient.

## Osteoarthritis of Knee

The degenerative process of osteoarthritis of the knee joint results from a gradual and progressive destruction of the articular cartilage and is mediated by metalloproteinases. These enzymes are produced by chondrocytes, which also produce the tissue inhibitors of metalloproteinases (TIMP) 1 and 2, but in amounts insufficient to counteract the proteolytic effect, thus producing overall cartilage destruction. Growth factors contained in alpha granules of platelets have been postulated to be chondro-protective and capable of improving the physiology in osteoarthritic joints. PDGF and TGF-1 are believed to up-regulate the production of endogenous hyaluronic acid levels. PRGF is also believed to be capable of regulating the levels of TIMPs. PRP has been used in patients of early osteoarthritis in an attempt to improve the cartilage structure and to slow down the progression of the disease.

Spaková *et al*.[40] conducted a RCT on 120 patients with Kellgren and Lawrence Grades 1, 2, or 3 osteoarthritis, comparing PRP injection with hyaluronic acid and concluded that autologous PRP was an effective and safe method in the treatment of the initial stages of knee osteoarthritis. Kon *et al*.[41] concluded that autologous PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function. Better results were achieved in younger and more active patients with a low degree of cartilage degeneration. Cerza *et al*.[42] published a RCT with 120 patients reported significantly better clinical outcome with autologous PRP than with HA, with sustained lower WOMAC scores. Patel *et al*.[43] published the results of a RCT conducted on 78 patients (156 knees) with bilateral osteoarthritis and reported improvement VAS scores for pain and in all parameters of WOMAC scores in patients who received PRP injections. The improvement reported was greater among patients with early osteoarthritis (Ahlback I). Importantly, all of these RCTs have reported a good safety profile of the PRP injections and no major complications whatsoever. Published studies of PRP use in knee osteoarthritis have been summarized in Table 5.

Osteoarthritis of the knee is one of the commonest degenerative diseases encountered in clinical practice and the prospect of arresting the disease process in its initial stages looks rewarding. The clinical evidences of PRP use in early knee osteoarthritis weighs in favor of PRP; one may offer PRP injections to early osteoarthritis patients but a definite recommendation cannot be made at this stage. Longer follow-ups of current studies would provide a better understanding of the actual benefits of PRP.

## Achilles Tendinopathy

Tendinopathies and tears of Achilles tendon are known to be difficult to heal and PRP has been used in attempts for enhancing healing at this site.

DeJonge *et al*.[44] studied 44 patients with chronic tendinopathy 2-7 cm proximal to the Achilles tendon

**Table 4: Summary of studies using PRP for rotator cuff injuries**

| Authors | Study type | Patients studied | Controls | Outcome measure | Follow up | Results |
|---|---|---|---|---|---|---|
| Randelli *et al*.[36] | RCT | 26 cases *vs.* 27 | Nonapplication of PRP | SST, UCLA score, Constant score | 3,6,12 and 24 months | PRP positively affected cuff rotator healing of grade 1 and 2 tears |
| Rha *et al*.[37] | RCT | | Dry needling | Shoulder pain and disability index, passive ROM | | clinical effect of the PRP injection was superior to the dry needling from six weeks to six months after initial injection |
| Weber *et al*.[38] | RCT | 30 cases *vs.* 30 | Nonapplication of PRP | UCLA score, VAS, SST, ASES score | 3,6,9 and 12 weeks | No significant difference in VAS scores between groups and no statistically significant differences in recovery of motion, SST or ASES scores |

RCTs = Randomized control trials, PRP = Platelet rich plasma, SST = Simple shoulder test, UCLA = University of California Los Angeles, VAS = Visual analogue score, ASES = American shoulder and elbow surgeons

**Table 5: Summary of studies using PRP for knee osteoarthritis**

| Authors | Study type | Patients studied | Control | Outcome measure | Followup | Results |
|---|---|---|---|---|---|---|
| Spakova *et al*.[40] | RCT | 60 cases *vs.* 60 controls | Hyaluronic acid | Pain score, WOMAC | 3 and 6 months | Statistically significantly better results in the PRP group for WOMAC and pain score |
| Kon *et al*.[41] | RCT | 50 PRP *vs.* 50 LWHA *vs.* 50 HWHA | Hyaluronic acid | IKDC, EQ-VAS, | 2 and 6 months | PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function |
| Cerza *et al*.[42] | RCT | 60 cases *vs.* 60 controls | Hyaluronic acid | WOMAC | 4,12 and 24 weeks | Significant effect shortly after the final infiltration of PRP and a continuously improving sustained effect up to 24 weeks |
| Patel *et al*.[43] | RCT | 26 single PRP *vs.* 25 double PRP *vs.* 27 NS | Normal Saline | VAS, WOMAC | 6 weeks, 3 and 6 months | Groups treated with PRP had better results than did the group injected with saline only |

RCTs = Randomized control trials, PRP = Platelet-rich plasma, VAS = Visual analogue score, LWHA = Low molecular weight hyaluronic acid, HWHA = High molecular weight hyaluronic acid, HA = Hyaluronic acid, NS = Normal Saline, IKDC = International knee documentation committee subjective knee form, EQ-VAS = Euro Qol visual analogue score, WOMAC = Western Ontario and McMaster Universities

insertion and injected them with PRP or saline and subjected the patients to an eccentric training program. One year of followup showed no clinical and ultrasonographic superiority of PRP injection over the placebo injection. deVos *et al*.[45] evaluated the tendon structure by ultrasonographic tissue characterization by a double-blind, randomized, placebo-controlled clinical trial in 54 patients; 27 patients received PRP injection and 27 received saline injection. After 24 weeks they concluded that PRP injections did not contribute to an increased tendon structure or altered the degree of neo-vascularization, compared with placebo. Owens *et al*.[46] reported modest improvement in functional outcome in 10 patients who had received PRP injection for mid substance Achilles tendinopathy. Monto *et al*.[47] reported clinical success in 28 out of 30 patients with recalcitrant Achilles tendinosis. The improvement noted was in the AOFAS score and the MR architecture of the tendon.

Enhancement of repair of the Achilles tendon tear with PRP has also been attempted. Though Sanchez *et al*.[26] reported good results in their case control study using platelet-rich matrices for the repair of ruptured Achilles tendon in 12 athletes, Schepull *et al*.[48] concluded that PRP was not useful for the treatment of Achilles tendon ruptures [Table 6].

In summary, the results of use of PRP in Achilles tendon disorders are not as encouraging as in other conditions. While most studies have reported disappointing results, few of the studies do show good results. Differences in PRP preparation and mode of application may be a contributing factor in providing such results. Additionally, each study has used a different outcome evaluation score that may also have some influence on the results. Last but not the least, the properties of the Achilles tendon itself (like the relatively large bulk of the tendon and it being subjected to eccentric loading) may contribute to poor efficacy of this method of treatment.

## Patellar Tendinopathy

Jumper's knee in athletes is a common cause of knee pain. Filardo *et al*.[49] evaluated the efficacy of PRP injections for refractory patellar tendinopathy and concluded that PRP injections had the potential to promote the achievement of a satisfactory clinical outcome, even in chronic refractory tendinopathy. Gosens *et al*.[50] reported on the pain and the activity levels before and after PRP injection in patellar tendinopathy in a prospective cohort study and concluded that patients treated with PRP showed a statistically significant improvement. Vetrano *et al*.[51] reported their results comparing PRP injections with extracorporeal shock wave therapy (ESWT) and reported a significantly better improvement in PRP group over the ESWT group after 12 months of followup [Table 7].

In summary, good results of PRP use in patellar tendinopathy have been reported but the studies published so far are poorly conducted. Only one RCT has been conducted till date and hence more studies with encouraging results are required before recommending PRP use in Patellar tendinopathy.

## Future of Platelet rich Plasma and Other Orthobiologics

Orthobiologics, especially PRP, hold a lot of promise as upcoming and novel treatment modalities. Although stem cells and ACS also appear interesting in theory, technical difficulties in preparation and use makes them rather user-unfriendly. If one analyzes the pros and cons of the available orthobiologics, it becomes clear that the lack of adequately powered studies is an important issue preventing their recommendation for routine use. However, even with the limited published scientific data, PRP appears to be the most attractive option available, with minimal side effects;

**Table 6: Summary of studies using PRP for Achilles tendinopathy**

| Authors | Study type | Patients studied | Controls | Outcome measure | Followup | Results |
|---|---|---|---|---|---|---|
| deJonge *et al*.[44] | RCT | 27 cases *vs.* 27 | Saline | VISA-A, Patient satisfaction and ultrasound | 6,12, 24 weeks and 1 year | No clinical or ultrasonographic benefit of PRP over placebo over 1 year period |
| deVos *et al*.[45] | RCT | 27 cases *vs.* 27 | Saline | Ultrasonographic evaluation | 6,12 and 24 weeks | PRP in the treatment of chronic midportion Achilles tendinopathy does not contribute to increased tendon structure or alter the degree of neovascularisation, compared with placebo |
| Owens *et al*.[46] | Retrospective | 10 | - | FAAM, SF-8, MRI | 2 years | Patients receiving PRP injection demonstrated modest improvement in functional outcome measures |
| Monto *et al*.[47] | Prospective Trial | 30 | - | AOFAS, MRI, Ultrasound | 1, 2, 3, 6, 12, and 24 months | Improvement in AOFAS score within 3 months which remained elevated at 24 months |
| Sanchez *et al*.[26] | case control | 6 cases *vs.* 6 | Nonapplication of PRP | ROM, functional recovery and ultrasound | Weekly for 1 month, 4 weekly for 6 months, 9 and 12 months | Early recovery of ROM and functional activities among atheletes receiving PRP than those not receiving it |
| Schepull *et al*.[48] | RCT | 16 cases *vs.* 14 | Nonapplication of PRP | Achilles Tendon Rupture Score, heel-raise index, 3D radiographs | 7, 19, and 52 weeks | PRP is not useful for treatment of Achilles tendon ruptures |

RCTs = Randomized control trials, PRP = Platelet-rich plasma, VISA-A = Victorian institute of sports assessment- achilles questionaire, FAAM = Foot and ankle ability measure, AOFAS = American orthopedic foot & ankle society, MRI = Magnetic resonance imaging, ROM = Range of motion

**Table 7: Summary of studies using PRP for patellar tendinopathy**

| Authors | Study type | Patients studied | Controls | Outcome measure | Followup (months) | Results |
|---|---|---|---|---|---|---|
| Filardo *et al*.[49] | Case control study | 15 cases *vs.* 16 controls | Physical therapy | Tegner, EQ VAS and pain level | 6 | Statistically significant improvement in all scores at the end of the PRP injections and a further improvement was noted at six months |
| Gosens *et al*.[50] | Prospective case series | 36 patients | - | VAS, VISA | - | Statistically significant improvement in VAS and VISA scores in patients receiving the PRP injections |
| Vetrano *et al*.[51] | RCT | 23 cases *vs.* 23 controls | Extra corporeal shock wave | VISA-P, VAS, modified Blazina scale | 2,6 and 12 | The PRP group showed significantly better improvement than the ESWT group in VISA-P, VAS scores at 6-and 12-month followup, and modified Blazina scale score at 12-month followup |

RCTs = Randomized control trials, EQ VAS = Euro Qol Visual analogue score, VAS = Visual Analogue Score, VISA = Victorian Institute of Sports Assessment, VISA-P = Victorian Institute of Sports Assessment- Patellar Questionaire, PRP = Platelet-rich plasma, ESWT = Extracorporeal shock wave therapy

the relative ease of preparation, cost effectiveness and the ability to complete the procedure as a day care procedure goes in favor of PRP. However, caution has to be advocated, as PRP preparation needs to be carried out in a sterile environment and preferably in bio-safety cabinets and the usage standardized. In India, autologous PRP therapy has been used in knee osteoarthritis,[43] nonunion,[52] lateral epicondylitis, rotator cuff injuries, plantar fasciitis, *etc*.[53] At a few centers it is being utilized for treatment of alopecia.[54] The blood banks of these centers are generally preparing the PRP for medical use; some surgeons are using commercially available kits also. However, there is lack of uniformity in the preparation methods amongst various centers and standardization of the final product is not adequately established. Additionally, there are concerns about the need for licensing to prepare such products because all blood banks need to obtain license from the Drug Controller General of India (DCGI) for their functioning, which is generally renewed every 5 years (Drugs and cosmetics act – 1940, MOHF, Government of India). Thus, having a well-equipped and licensed set up for preparation of the PRP is essential. Commercial PRP preparation systems like Biomet GPSIII (Biomet Inc, Warshaw, USA), Arthrex ACP Double syringe system (Arthrex Inc, Naples, USA), RegenPRP (Regen Lab, Switzerland) etc., have yet to become popular in India. This probably is due to the licensing requirements and the cost involved in the use of such systems. The cost of PRP preparation with these systems is somewhere between USD 500 and 1000.[55]

It is pertinent to mention here that the WADA (World Anti Doping Agency) included PRP in its list of prohibited substances for the year 2010; subsequently in the year 2011 WADA clarified that even though PRP contains growth factors, PRP use in sports injuries is not prohibited. Nevertheless, this episode of banning PRP use in sportsmen and then lifting off the ban, brought significant negative publicity to PRP for routine use.[56]

What is required at present is an international regulatory authority, which would lay down guidelines for the preparation, handling and use of PRP. The International Cellular Medical Society (ICMS) asserts that a need exists to create standards for PRP preparations, techniques and tracking and has prepared a protocol for the same.[57] Quality control regulating the minimum amount of growth factors in the prepared products would also be a welcome addition. Any future trials should follow standardized guidelines and ethics or other relevant committee approval regarding the methodology of PRP preparation and use; the results could be analyzed and made available through the committee also. These few quality control and regulatory steps may lead to more scientific and rational usage of PRP, in well-regulated environments. It may also be noted that it is still illegal for a medical practitioner to charge money for PRP injection in South Korea.[58]

## References


1. Kannus P, Natri A. Etiology and pathophysiology of tendon ruptures in sports. Scand J Med Sci Sports 1997;7:107-12.
2. Available from: http://orthoinfo.aaos.org/topic.cfm?topic=A00525 [Last accessed on 25th Nov. 2013].
3. Roberts TT, Rosenbaum AJ. Bone grafts, bone substitutes and orthobiologics: The bridge between basic science and clinical advancements in fracture healing. Organogenesis 2012;8:114-24.
4. Paoloni J, De Vos RJ, Hamilton B, Murrell GA, Orchard J. Platelet-rich plasma treatment for ligament and tendon injuries. Clin J Sport Med 2011;21:37-45
5. Wehling P, Moser C, Frisbie D, McIlwraith CW, Kawcak CE, Krauspe R, *et al*. Autologous conditioned serum in the treatment of orthopedic diseases: The orthokine therapy. Bio Drugs 2007;21:323-32
6. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: A review of the literature. J Bone Joint Surg Br 2009;91:987-96.
7. Schmitt A, vanGriensven M, Imhoff AB, Buchmann S. Application of stem cells in orthopedics. Stem Cells Int 2012;2012:394962.
8. Leadbetter WB. Cell-matrix response in tendon injury. Clin Sports Med 1992;11:533-78.
9. Gelberman R, Goldberg V, An KN, BanesA. Tendon. In: Woo SL, Buckwalter JA, (editors). Injury and Repair of the Musculoskeletal Soft Tissues: Workshop, Savannah, Georgia, 1987. Park Ridge, Illinois: American Academy of Orthopaedic Surgeons; 1988. p. 1-40.
10. Filardo G, Kon E, Di Martino A, DiMatteo B, Merli ML, Cenacchi A, *et al*. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord 2012;13:229.
11. Gibble J, Ness P. Fibrin glue: The perfect operative sealant? Transfusion 1990;30:741-7.
12. Marx RE, Carlson ER, Eichstaedt RM, SchimmeleSR, Strauss JE, Georgeff KR. Platelet-rich plasma – Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-46.
13. Edwards SG, Calandruccio JH. Autologous blood injections for refractory lateral epicondylitis. J Hand Surg Am 2003;28:272-8.
14. Connell DA, Ali KE, Ahmad M, Lambert S, Corbett S, Curtis M. Ultrasound-guided autologous blood injection for tennis elbow. Skeletal Radiol 2006;35:371-7.
15. Ozturan KE, Yucel I, Cakici H, Guven M, Sungur I. Autologous blood and corticosteroid injection and extracorporeal shock wave therapy in the treatment of lateral epicondylitis. Orthopedics 2010;33:84-91.
16. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: A prospective, double-blind, randomized trial of autologous blood injections versus platelet-rich plasma injections. Br J Sports Med 2011;45:966-71.
17. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: A randomized controlled clinical trial. Am J Sports Med 2011;39:2130-4.
18. Kazemi M, Azma K, Tavana B, RezaieeMoghaddam F, Panahi A. Autologous blood versus corticosteroid local injection in the short-term treatment of lateral elbow tendinopathy: A randomized clinical trial of efficacy. Am J Phys Med Rehabil 2010;89:660-7.
19. Suresh SP, Ali K, Jones H, Connell DA. Medial epicondylitis: Is ultrasound guided autologous blood injection an effective treatment? Br J Sports Med 2006;40:935-9.
20. James SL, Ali K, Pocock C, Robertson C, Walter J, Bell J, *et al*. Ultrasound guided dry needling and autologous blood injection for patellar tendinosis. Br J Sports Med 2007;41:518-21.
21. Becker C, Heidersdorf S, Drewlo S, de Rodriguez SZ, Kramer J, Willburger RE. Efficacy of epidural perineural injections with autologous conditioned serum for lumbar radicular compression: An investigator-initiated, prospective, double-blind, reference-controlled study. Spine (Phila Pa 1976) 2007;32:1803-8.
22. Moser CB, Jansen SA. Autologous conditioned serum (ACS) Injection compared to HA and saline injections for the treatment of knee OA. American Academy of Orthopedic Surgeons 74th Annual Meeting 2007; 14-18
23. Hernigou P, Mathieu G, Poignard A, Manicom O, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Surgical technique. J Bone Joint Surg Am 2006;88(Suppl 1 Pt 2):322-7.
24. Kotobuki N, Hirose M, Takakura Y, Ohgushi H. Cultured autologous human cells for hard tissue regeneration: Preparation and characterization of mesenchymal stem cells from bone marrow. Artif Organs 2004;28:33-9.
25. Harrison P, Cramer EM. Platelet alpha-granules. Blood Rev 1993;7:52-62.
26. Sanchez M, Anitua E, Azofra J, Andia I, Padilla S, Mujika I. Comparison of surgically repaired achilles tendon tears using platelet-rich fibrin matrices. Am J Sports Med 2007;35:245-51.
27. Mishra A, Harmon K, Woodall J, Vieira A. Sports Medicine Applications of Platelet Rich Plasma. Curr Pharm Biotechnol 2012;13:1185-95.
28. Dragoo JL, Braun HJ, Durham JL, Ridley BA, Odegaard JI, Luong R, *et al*. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. Am J Sports Med 2012;40:1274-81.
29. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of

tendinopathy. J Bone Joint Surg Am 2012;94:e143 (1-8).
30. Taylor DW, Petrera M, Hendry M, The odoropoulos JS. A systematic review of the use of platelet-rich plasma in sports medicine as a new treatment for tendon and ligament injuries. Clin J Sport Med 2011;21:344-52.
31. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet rich plasma. Am J Sports Med 2006;34:1774-8.
32. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: Platelet-rich plasma versus corticosteroid injection with a 1-year followup. Am J Sports Med 2010;38:255-62.
33. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: A double-blind randomized controlled trial with 2-year followup. Am J Sports Med 2011;39:1200-8.
34. Chaudhury S, de La Lama M, Adler RS, Gulotta LV, Skonieczki B, Chang A, *et al*. Platelet-rich plasma for the treatment of lateral epicondylitis: Sonographic assessment of tendon morphology and vascularity (pilot study). Skeletal Radiol 2013;42:91-7.
35. Randelli PS, Arrigoni P, Cabitza P, Volpi P, Maffulli N. Autologous platelet rich plasma for arthroscopic rotator cuff repair: A pilot study. Disabil Rehabil 2008;30:1584-9.
36. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: A prospective RCT study, 2-year followup. J Shoulder Elbow Surg 2011;20:518-28.
37. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: A randomized controlled trial. Clin Rehabil 2013;27:113-22.
38. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-Rich Fibrin Matrix in the Management of Arthroscopic Repair of the Rotator Cuff: A Prospective, Randomized, Double-Blinded Study. Am J Sports Med 2013;41:263-70.
39. Castricini R, Longo UG, De Benedetto M, Panfoli N, Pirani P, Zini R, *et al*. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: A randomized controlled trial. Am J Sports Med 2011;39:258-65.
40. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil 2012;91:411-7.
41. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, *et al*. Platelet-rich plasma intraarticular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. Arthroscopy 2011;27:1490-501.
42. Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, *et al*. Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intraarticular Infiltration in the Treatment of Gonarthrosis. Am J Sports Med 2012;40:2822-7.
43. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. Am J Sports Med 2013;41:356-64.
44. deJonge S, de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, *et al*. One-year followup of platelet-rich plasma treatment in chronic Achilles tendinopathy: A double-blind randomized placebo-controlled trial. Am J Sports Med 2011;39:1623-9.
45. De VosRJ, Weir A, Tol JL, Verhaar JA, Weinans H, van Schie HT. No effects of PRP on ultrasonographic tendon structure and neovascularisation in chronic midportion Achilles tendinopathy. Br J Sports Med 2011;45:387-92.
46. Owens RF Jr, Ginnetti J, Conti SF, Latona C. Clinical and magnetic resonance imaging outcomes following platelet rich plasma injection for chronic mid-substance Achilles tendinopathy. Foot Ankle Int 2011;32:1032-9.
47. Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. Foot Ankle Int 2012;33:379-85.
48. Schepull T, Kvist J, Norrman H, Trinks M, Berlin G, Aspenberg P. Autologous platelets have no effect on the healing of human achilles tendon ruptures: A randomized single-blind study. Am J Sports Med 2011;39:38-47.
49. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int Orthop 2010;34:909-15.
50. Gosens T, Den Oudsten BL, Fievez E, van 't Spijker P, Fievez A. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar tendinopathy: A prospective cohort study and the influence of previous treatments. Int Orthop 2012;36:1941-6.
51. Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-Rich Plasma Versus Focused Shock Waves in the Treatment of Jumper's Knee in Athletes. Am J Sports Med 2013;41:795-803.
52. Malhotra R, Kumar V, Trikha A. Platelet Concentrate in Treatment of Non Union of Long Bones. In proceedings of AAOS Annual Meeting. Feb 2012.
53. Available from: http://www.eternesseclinic.com/platelet-rich-plasma-therapy/[last accessed on 2013 Nov 25].
54. Available from: http://www.apollodermatologistdelhi.com/new_projects.html [last accessed on 2013 Nov 25].
55. Available from: http://orthopedics.about.com/od/injectio2/p/prp.htm [last accessed on 2013 Nov 25].
56. Available from: http://www.usada.org/prohibited-list/athlete-guide/[last accessed on 2013 Nov 25].
57. Guidelines for the Use of Platelet Rich Plasma Available from: http://www.cellmedicinesociety.org/icms-guidelines [last accessed on 2013 Nov 25].
58. Park YG, Han SB, Song SJ, Kim TJ, Ha CW. Platelet-rich plasma therapy for knee joint problems: Review of the literature, current practice and legal perspectives in Korea. Knee Surg Relat Res 2012;24:70-8.

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