

## **The Application of [Platelet Rich Plasma \(PRP\)](#) in Various Fields and How to Choose PRP Rich in White Blood Cells (L-PRP) and PRP Poor in White Blood Cells (P-PRP)**

The recent discovery of a large number of high-quality evidence supports the use of LR-PRP injection for the treatment of lateral Epicondylitis and LP-PRP for the treatment of knee Articular bone. Medium quality evidence supports the use of LR-PRP injection for patellar tendinosis and PRP injection for Plantar fasciitis and donor site pain in patellar tendon transplantation BTB ACL reconstruction. There is not enough evidence to routinely recommend PRP for rotator cuff tendinosis, hip Articular bone osteoarthritis or high ankle sprain. Current evidence suggests that PRP lacks efficacy in treating Achilles tendon disease, muscle injury, acute fractures or bone non union, enhanced rotator cuff repair surgery, Achilles tendon repair, and ACL reconstruction.

Platelet rich plasma (PRP) is an autologous human plasma preparation that increases platelet concentration by centrifuging a large amount of the patient's own blood. Platelets in its  $\alpha$  Particles (TGF-  $\beta$  1, PDGF, bFGF, VEGF, EGF, IGF-1) contain an excessive amount of growth factors and mediators, which are concentrated through a centrifugation process to release suprabiological amounts of these growth factors and cytokines to the injured site and enhance the natural healing process.

The normal platelet count range is 150000 to 350000/  $\mu$  L. The improvement in bone and soft tissue healing has been demonstrated, with concentrated platelets reaching up to 1000000/  $\mu$  L. Represents a three to five fold increase in growth factors. PRP preparations are usually further divided into PRP rich in white blood cells (LR-PRP), defined as neutrophil concentration above baseline, and PRP poor in white blood cells (LP-PRP), defined as white blood cell (neutrophil) concentration below baseline.

### **Treatment of Tendon Injuries**

The use of PRP for the treatment of tendon injury or tendon disease has become a topic of multiple studies, and many cytokines found in PRP are involved in signaling pathways that occur during the healing stage of inflammation, cell proliferation, and subsequent tissue remodeling. PRP can also promote the formation of new blood vessels, which can increase the blood supply and nutrition required for cell regeneration of damaged tissue, as well as bring in new cells and remove debris from damaged tissue. These mechanisms of action may be particularly relevant to chronic tendinosis, where biological conditions are not conducive to tissue healing. A recent systematic review and meta-analysis concluded that injecting PRP can effectively treat symptomatic tendinosis.

### **Lateral Epicondylitis**

PRP has been evaluated as a potential treatment option for patients with lateral Epicondylitis who are not effective in physiotherapy. In the largest such study, Mishra et al. In a prospective Cohort study, 230 patients who did not respond to Conservative management of lateral Epicondylitis for at least 3 months were evaluated. The patient received LR-PRP treatment, and at 24 weeks, LR-PRP injection was associated with a significant improvement in pain compared to the control group (71.5% vs 56.1%,  $P=0.019$ ), as well as a significant decrease in the percentage of patients reporting residual elbow tenderness (29.1% vs 54.0%,  $P=0.009$ ). At 24 weeks, patients treated with LR-PRP showed clinically significant and statistically significant improvements compared to active control injections of local anesthetics.

Previous studies have shown that LR-PRP can also provide longer lasting relief for the symptoms of lateral Epicondylitis compared with Corticosteroid injection, so it has a more sustainable therapeutic effect. PRP seems to be an effective method for the treatment of external Epicondylitis. High quality evidence shows short-term and long-term efficacy. The best available evidence clearly indicates that LR-PRP should be the first treatment method.

### **Patellar Tendinosis**

Randomized controlled studies support the use of LR-PRP for the treatment of chronic refractory patellar tendon disease. Draco et al. Twenty three patients with patellar tendinosis who failed Conservative management were evaluated. Patients were randomly assigned to receive ultrasound-guided individual dry needles or injection of LR-PRP, and were followed up for >26 weeks. Through VISA-P measurement, the PRP

treatment group showed significant improvement in symptoms at 12 weeks ( $P=0.02$ ), but the difference was not significant at  $>26$  weeks ( $P=0.66$ ), indicating that the benefits of PRP for patellar tendon disease may be an improvement in early symptoms. Vitrano et al. The benefits of PRP injection in treating chronic refractory patellar tendon disease compared to focused extracorporeal shock wave therapy (ECSWT) were also reported. Although there was no significant difference between the groups during the 2-month follow-up, the PRP group showed statistically significant improvement at 6 and 12 months of follow-up, surpassing ECSWT as measured by VISA-P and VAS, and measuring the Blazina scale score at 12 months of follow-up (all  $P<0.05$ ).

This review evaluates the current clinical literature on the use of platelet-rich plasma (PRP), including leukocyte rich PRP (LR PRP) and leukocyte poor PRP (LP PRP), in order to develop evidence-based recommendations for various musculoskeletal diseases.

The recent discovery of a large number of high-quality evidence supports the use of LR-PRP injection for the treatment of lateral Epicondylitis and LP-PRP for the treatment of knee Articular bone. Medium quality evidence supports the use of LR-PRP injection for patellar tendinosis and PRP injection for Plantar fasciitis and donor site pain in patellar tendon transplantation BTB ACL reconstruction. There is not enough evidence to routinely recommend PRP for rotator cuff tendinosis, hip Articular bone osteoarthritis or high ankle sprain. Current evidence suggests that PRP lacks efficacy in treating Achilles tendon disease, muscle injury, acute fractures or bone non union, enhanced rotator cuff repair surgery, Achilles tendon repair, and ACL reconstruction.

## **Introduce**

Platelet rich plasma (PRP) is an autologous human plasma preparation that increases platelet concentration by centrifuging a large amount of the patient's own blood. Platelets in its  $\alpha$  Particles (TGF-  $\beta$  1. PDGF, bFGF, VEGF, EGF, IGF-1) contain an excessive amount of growth factors and mediators, which are concentrated through a centrifugation process to release suprabiological amounts of these growth factors and cytokines to the injured site and enhance the natural healing process. The normal platelet count range is 150000 to 350000/  $\mu$  L. The improvement in bone and soft tissue healing has been demonstrated, with concentrated platelets reaching up to 1000000/  $\mu$  L. Represents a three to five fold increase in growth factors.

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## **Preparation and Composition**

There is no general consensus on the optimal PRP formulation for blood component concentration, and there are currently many different commercial PRP systems on the market. Therefore, according to different commercial systems, there are differences in PRP collection protocols and preparation characteristics, giving each PRP system unique attributes. Commercial systems typically differ in platelet capture efficiency, separation method (one-step or two-step centrifugation), centrifugation speed, and type of collection tube system and operation. Usually, before centrifugation, whole blood is collected and mixed with anticoagulant factors to separate red blood cells (RBCs) from platelet-poor plasma (PPP) and the "erythrocyte sedimentation brown layer" containing concentrated platelets and white blood cells. Various methods are used to separate platelets, which can be directly injected into the patient's body or "activated" by adding calcium chloride or thrombin, leading to platelet degranulation and release of growth factors. Two patient-specific factors, including drug administration and commercial system preparation methods, affect the specific composition of PRP, as well as this change in the composition of PRP formulations in explaining the clinical efficacy of PRP.

Our current understanding is that PRP with increased white blood cell content, namely PRP rich in white blood cells (neutrophils), is associated with pro-inflammatory effects. The increased concentration of white blood cells (neutrophils) in LR-PRP is also

associated with an increase in catabolic cytokines, such as interleukin-1  $\beta$ , Tumor Necrosis Factor  $\alpha$  And metalloproteinases, which may antagonize the anabolic cytokines contained in platelets. The clinical consequences and cellular effects of these different PRP formulations, including white blood cell content, are still being elucidated. This review aims to evaluate the best quality evidence available for various clinical indications of different PRP formulations.

### **Achilles Tendon Disease**

Several historical trials have failed to show differences in clinical outcomes between PRP and placebo alone in the treatment of Achilles tendinitis. A recent Randomized controlled trial compared a series of four LP-PRP injections with a placebo injection combined with a centrifugal load rehabilitation program. Compared with the placebo group, the PRP treatment group showed significant improvements in pain, function, and activity scores at all time points throughout the 6-month follow-up period. The study also found that a single large volume injection (50 mL) of 0.5% Bupivacaine (10 mL), methylprednisolone (20 mg) and physiological saline (40 mL) had comparable improvements, but when considering this treatment, care should be taken in view of the increased risk of tendon rupture after steroid injection.

### **Rotator Cuff Tendinosis**

There are few high-level studies on PRP injection in the non-surgical treatment of rotator cuff tendon disease. A few published studies have compared the clinical results of subacromial injection of PRP with placebo and Corticosteroid, and no study has evaluated the direct injection of PRP into the tendon itself. Casey Buren et al. It was found that there was no difference in clinical outcome scores compared to injecting physiological saline under the shoulder peak. However, a Randomized controlled trial found that two injections of LR-PRP every four weeks improved pain compared with placebo injections. Shams et al. The comparable improvement of subacromial PRP and Corticosteroid injection between Xi'an Ontario RC index (WORI), shoulder pain disability index (SPDI) and VAS shoulder pain and Neer test was reported.

So far, research has shown that injecting PRP under the shoulder peak has a significant improvement in the reported results of patients with rotator cuff tendon disease. Other studies that require longer follow-up, including evaluating direct injection of PRP into tendons. These PRP injections have been shown to be safe and may be an alternative to Corticosteroid injections in rotator cuff tendinosis.

### **Plantar Fasciitis**

Several Randomized controlled trial evaluated PRP injection for chronic Plantar fasciitis. The potential of PRP as a local injection therapy alleviates concerns related to the injection of Corticosteroid, such as atrophy of fat pads or rupture of plantar fascia. Two recent meta-analyses evaluated the comparison between PRP injection and Corticosteroid injection, and concluded that PRP injection is a feasible alternative to Corticosteroid injection in terms of efficacy. Some studies have proved the superiority of PRP.

## **Surgery combined with PRP**

### **Shoulder Sleeve Repair**

Several high-level clinical studies evaluated the use of PRP products in Arthroscopy repair of rotator cuff tears. Many studies have specifically studied the use of platelet rich fibrin matrix preparations for enhancement (PRFM), while other studies have injected PRP directly into the repair site. There is significant heterogeneity in PRP or PRFM formulations. Patient oriented results were obtained, such as the University of California, Los Angeles (UCLA), American Shoulder and Elbow Association (ASES), Constant Shoulder Score, Simple Shoulder Test (SST) score, and VAS pain score, as well as objective clinical data such as rotator cuff strength and shoulder ROM were collected to measure differences in functional outcomes. Most individual studies have shown little difference in the measures for these results in PRP compared with individual repair [such

as the pads for Arthroscopy rotator cuff repair. In addition, the large meta-analysis and recent rigorous review have proved that Arthroscopy repair of shoulder cuff [PRP] has no significant benefit in breast augmentation. However, limited data show that it has some effect in reducing perioperative pain, which is likely due to the anti-inflammatory properties of PRP.

Subgroup analysis showed that in the middle and small tears treated with Arthroscopy double row repair, injection of PRP could reduce the re-tearing rate, thus achieving better results. Qiao et al. It was found that PRP is beneficial in reducing the rate of re-tearing of moderate and large rotator cuff tears compared to surgery alone.

Randomized clinical trials and large-scale meta-analysis indicate a lack of evidence for the use of PRP and PRFM as reinforcement for rotator cuff repair. Some subgroup analyses suggest that double row repair may have some benefits for treating small or moderate tears. PRP may also help to immediately alleviate postoperative pain.

### **Achilles Tendon Repair**

Preclinical studies have shown that PRP has a promising effect on promoting the healing of Achilles tendon rupture. However, conflicting evidence hinders the conversion of PRP as an effective adjuvant therapy for acute Achilles tendon rupture in humans. For example, in one study, the structural and functional outcomes of patients with Achilles tendon rupture treated with and without PRP were the same. In contrast, Zou et al. In a prospective randomized controlled study, 36 patients were recruited who underwent acute Achilles tendon rupture repair with and without intraoperative injection of LR-PRP. Patients in the PRP group had better isokinetic muscles at 3 months, and had higher SF-36 and Leppilahti scores at 6 and 12 months, respectively (all  $P < 0.05$ ). In addition, the ankle joint range of motion in the PRP group also significantly improved at all time points at 6, 12, and 24 months ( $P < 0.001$ ). Although more high-quality clinical trials are needed, injecting PRP as a surgical enhancement for acute Achilles tendon repair does not seem to be beneficial.

### **Anterior Cruciate Ligament Surgery**

The success of anterior cruciate ligament (ACL) surgery depends not only on technical factors (such as graft tunnel placement and graft fixation), but also on the biological healing of ACL grafts. The research on the use of PRP in ACL reconstruction surgery focuses on three biological processes: (1) the integration of bone ligaments between the graft and the tibial and femoral tunnels, (2) the maturation of the joint portion of the graft, and (3) healing and pain reduction at the harvesting site.

Although multiple studies have focused on the application of PRP injection in ACL surgery in the past five years, there have been only two high-level studies. Previous studies have shown that mixed evidence supports the integration of transplant or graft mature Osteoligamentous cells using PRP injection, but some evidence has been shown to support pain in the donor site. Regarding the use of PRP enhancement to improve graft bone tunnel bonding, recent data shows that PRP has no clinical benefits in tunnel widening or bone integration of grafts.

Recent clinical trials have shown promising early results in donor site pain and healing using PRP. Sajas et al. Observing the anterior knee pain after autologous ACL reconstruction of bone patella bone (BTB), it was found that compared with the control group, the anterior knee pain was reduced during a 2-month follow-up.

More research is needed to investigate the effects of PRP on ACL graft integration, maturation, and donor site pain. However, at this point, studies have shown that PRP has no significant clinical impact on graft integration or maturation, but limited studies have shown positive results in reducing pain in the patellar tendon donor area.

### **Osteoarthritis**

People are more and more interested in the efficacy of PRP intra-articular injection in the non-surgical treatment of knee Articular bone osteoarthritis. Shen et al. A meta-analysis of 14 randomized clinical trials (RCTs) including 1423 patients was conducted to compare PRP with various controls (including placebo, hyaluronic acid, Corticosteroid injection, oral medicine and Homeopathy treatment). Meta analysis showed that during the follow-up of 3, 6 and 12 months, the score of Osteoarthritis index (WOMAC) of Western Ontario University and McMaster University improved significantly ( $=0.02$ ,

0.04, <0.001, respectively). A subgroup analysis of PRP efficacy based on the severity of knee osteoarthritis showed that PRP is more effective in patients with mild to moderate OA. The author believes that in terms of pain relief and patient reported results, intra articular PRP injection is more effective than other alternative injections in treating knee osteoarthritis.

Riboh et al. conducted a meta-analysis to compare the role of LP-PRP and LR-PRP in the treatment of knee Osteoarthritis, and found that compared with HA or placebo, LP-PRP injection could significantly improve the WOMAC score. Ferrado et al. studied LR-PRP injection, or found that there was no statistical difference compared with HA injection, further proving that LP-PRP may be the first choice for the treatment of Osteoarthritis symptoms. Its biological basis may lie in the relative levels of inflammation and anti-inflammatory mediators present in LR-PRP and LP-PRP. In the presence of LR-PRP, the inflammatory mediator TNF-  $\alpha$ , IL-6, IFN-  $\gamma$  And IL-1  $\beta$  Significantly increased, while injection of LP-PRP increases IL-4 and IL-10, which are anti-inflammatory mediators. It is found that IL-10 is particularly helpful in the treatment of hip osteoarthritis, and may also inhibit the inflammatory mediator TNF-  $\alpha$ , IL-6 and IL-1  $\beta$  Release and block the inflammatory pathway by neutralizing nuclear factor kB activity. In addition to its harmful effects on chondrocytes, LR-PRP may also be unable to help treat Osteoarthritis symptoms due to its effects on synovial cells. Braun et al. It was found that treating synovial cells with LR-PRP or red blood cells can lead to significant pro-inflammatory mediator production and cell death.

Intra articular injection of LP-PRP is a safe treatment method, and there is Level 1 evidence that it can reduce the pain symptoms and enhance the function of patients diagnosed with knee Articular bone osteoarthritis. Larger scale and longer follow-up studies are needed to determine its long-term efficacy.

### **Hip Osteoarthritis**

Only four randomized clinical trials compared PRP injection and hyaluronic acid (HA) injection for the treatment of hip osteoarthritis. The outcome indicators are VAS pain score, WOMAC score, and Harris hip joint score (HHS).

Batalya et al. found significant improvements in VAS scores and HHS at 1, 3, 6, and 12 months. A peak improvement occurred at 3 months, and the effect gradually weakened thereafter [72]. The score at 12 months still significantly improved compared to the baseline score ( $P < 0.0005$ ); However, there was no statistically significant difference in results between the PRP and HA groups.

Di Sante et al. saw that the VAS score of the PRP group improved significantly at 4 weeks, but recovered to the baseline at 16 weeks. There was no significant difference in VAS scores between the HA group at 4 weeks, but there was a significant improvement at 16 weeks. Dalari et al. We evaluated the impact of PRP on HA injection, but also compared the combination of HA and PRP injection for both cases. The PRP group was found to have the lowest VAS score among all three groups at all follow-up time points (2 months, 6 months, and 12 months). PRP also had significantly better WOMAC scores at 2 and 6 months, but not at 12 months. Doria et al. A double-blind randomized clinical trial was conducted to compare patients who received three consecutive weekly injections of PRP and three consecutive injections of HA. This study found improvements in HHS, WOMAC, and VAS scores in the HA and PRP groups during 6 and 12 month follow-up. However, at all time points, there was no significant difference between the two groups. No research has shown that intra-articular injection of PRP into the hip has adverse effects, and all have concluded that PRP is safe.

Although the data is limited, intra-articular injection of PRP in the treatment of hip Articular bone osteoarthritis has been proved to be safe, and has certain efficacy in reducing pain and improving function, as measured by the results scores reported by patients. Multiple studies have shown that PRP can initially better alleviate pain compared to HA; However, as PRP and HA have very similar efficacy at 12 months, any initial advantage seems to weaken over time. Since a few clinical studies have evaluated the application of PRP in hip OA, more high-level evidence is needed to determine whether PRP can be used as an alternative to Conservative management to delay the operation of hip Articular bone osteoarthritis.

### **Ankle Sprain**

Only two randomized clinical trials that met our inclusion criteria evaluated the application of PRP in acute ankle sprain. Roden et al. A double-blind placebo-controlled randomized clinical trial was conducted on patients with acute ankle sprain in ED, comparing ultrasound guided injection of local anesthetic LR-PRP with saline and local anesthetic injection. They found no statistically significant difference in VAS pain score or lower limb function scale (LEFS) between the two groups.

Laval et al. randomly assigned 16 elite athletes diagnosed with high ankle sprains to receive ultrasound-guided LP-PRP injection treatment at the initial treatment stage, and repeated injections of a combined rehabilitation plan or a separate rehabilitation plan 7 days later. All patients received the same rehabilitation treatment protocol and regression criteria. The study found that the LP-PRP group resumed competition in a shorter period of time (40.8 days vs. 59.6 days,  $P < 0.006$ ).

PRP seems to be ineffective for acute ankle sprain. Although limited evidence suggests that LP-PRP injection may affect the high ankle of elite athletes.

### **Muscle Injury**

The use of PRP for treating muscle injury has shown ambiguous clinical evidence. Similar to tendon healing, the steps of muscle healing include the initial inflammatory response, followed by cell proliferation, differentiation, and tissue remodeling. Hamid et al. A single blind randomized study was conducted on 28 patients with grade 2 hamstring injury, comparing injection of LR-PRP with rehabilitation plans and rehabilitation alone. The group receiving LR-PRP treatment was able to recover from competition faster (average time in days, 26.7 vs. 42.5,  $P = 0.02$ ), but did not achieve structural improvement. In addition, significant placebo effects in the treatment group may confound these results. In a double-blind Randomized controlled trial, Reurink et al. We evaluated 80 patients and compared PRP injection with placebo saline injection. All patients received standard rehabilitation treatment. The patient was followed up for 6 months and there was no significant difference in terms of recovery time or re injury rate. The ideal PRP formula for improving muscle healing in clinically relevant ways is still elusive and future research should be conducted.

### **Management of Fractures and Non Union**

Although there is reasonable preclinical evidence to support the use of PRP to improve bone healing, there is no clinical consensus to support the routine use of PRP to promote bone healing. A recent review on PRP and acute fracture treatment highlighted three RCTs that did not demonstrate benefits in terms of functional outcomes, while two studies showed superior clinical outcomes. Most of the trials in this review (6/8) studied the efficacy of PRP in combination with other biological agents (such as mesenchymal stem cells and/or bone grafts) to promote fracture healing.

The working principle of platelet-rich plasma (PRP) is to provide growth factors and cytokines contained in platelets with an excess physiological quantity. In musculoskeletal medicine, PRP is a promising treatment method with clear safety evidence. However, the evidence of its efficacy is mixed and highly dependent on the ingredients and specific indications. More high-quality and large-scale clinical trials in the future are crucial for shaping our perspective on PRP.

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