# The Role of Platelet-rich Plasma in Rotator Cuff Repair

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**Abstract:** The shoulder is a common source of disability resulting from traumatic and degenerate tears of the rotator cuff, subacromial impingement, and osteoarthritis. Nonoperative management has focused on treatment of the predisposing factors, the use of analgesics and anti-inflammatory medication usually in association with local anesthetic and steroid injections. Surgical intervention allows debridement of the degenerate cuff and partial thickness cuff tears, subacromial bursitis, impinging bone spurs and osteophytes together with rotator cuff repairs. Repairs of degenerate and torn tissue are often prone to failure due to many intrinsic and extrinsic factors. It is assumed that some biological therapies might improve clinical, mechanical, and histologic outcomes. Injections of platelet-rich plasma (PRP) have led to reduced pain and improved recovery in other degenerate pathologies areas together with the restoration of function. This study reviews the current literature on PRP and in particular discusses its relevance in the treatment of rotator cuff tears.

**Key Words:** rotator cuff, PRP, PRGF

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The rotator cuff of the shoulder is affected by pathology common to all tendon bone insertional sites. Degenerative disease at the neighboring acromioclavicular joint, subacromial bursitis, and impingement from the overlying acromial arch all influence the tendons forming the rotator cuff. The tendon just proximal to its insertion is prone to tendinopathic degeneration, tears, and rupture. The frequency of tears has been shown to increase with increasing age.[1]

The management of rotator cuff tears is complex and multifactorial. Partial thickness tears may heal with conservative management and treatment of the predisposing factors. These may include abnormal shoulder biomechanics, debridement of bursae, boney subacromial spurs, and osteophytes.[2]

Operative treatment allows primary repairs to be performed either as an open or arthroscopic procedure. The repair tissue frequently degenerate and is of poor quality.[3,4]

Surgeons may augment the repairs using tendon autograft, allograft, xenograft, and even synthetic tissue.[5]

Platelet-rich plasma (PRP) presents an attractive option to improve and accelerate healing by concentrating the factors which enhance healing in normal healing tissues. This may be applied either by direct injection of PRP for nonoperatively managed tears or intraoperatively either at arthroscopic surgery or by physical application of a PRP matrix scaffold to repaired tissues.[6,7]

PRP application has developed from the use of autologous blood injections to promote healing; however, there is now growing evidence that it is the specific growth factors contained within the blood to promote healing. There is also increased evidence against whole blood injections.[8]

Platelets are cytoplasmic fragments of megakaryocyte leukocytes, lack nucleoli but contain mitochondria, microtubules, and granules. They have been shown to contain many biological active factors, which promote hemostasis, the synthesis of new connective tissue, and revascularization. The $\alpha$ granules, numbering approximately 50 to 80 per platelet, contain the bioactive proteins, which promote healing termed as growth factors.[9]

PRP and preparations rich in growth factors are obtained by the centrifugation of whole blood into its component fractions. This process was first described in 1999 by a research group in Vitoria, Spain.[10]

The term PRP may be applied to any fraction of autologous blood, which has a higher concentration of platelet concentration above that of the baseline.[11,12] The centrifugation process allows the separation of blood into its component cells and serum. Depending on the system used, white cells may be removed, resulting in a pure form of PRP termed, preparation rich in growth factors (Fig. 1). Some techniques are unable to separate the leukocytes from the sample. Neutrophils are now considered to lead to additional muscle damage after the original injury and there is no evidence that they play a beneficial role in muscle repair or regeneration.[13]

Differing centrifugation techniques also vary the volume and concentration of serum, platelets, and growth factors yielded. Typically, 10% of the initial volume of autologous blood is yielded as PRP concentrate after centrifugation. It has been stated that a therapeutic dose of PRP would need to be at least 3 to 6 times higher than the normal baseline.[14,15] Higher concentrations have been shown to have inhibitory effects.[16] Food consumed and the state of hydration of the patient before venusection also influences the sample of PRP produced. For consistency, patients are asked to fast for 3 to 4 hours before the blood samples are taken.

The volume and timing of the application vary according to the concentration and activation of the platelet components. After production, the sample of serum undergoes change and begins to coagulate. The platelets start secreting growth factors immediately and after 10 minutes the rate of production decreases, with the majority of pre-synthesized growth factors secreted within the first hour.[17,18] Sodium citrate is added to the serum to delay clotting and then calcium chloride reactivates the sample before clinical application. The administered platelets will go on to synthesize and secrete additional growth factors for 7 to 10 days. Although the initial burst is short lived, it has prolonged efficacy.[18,19]

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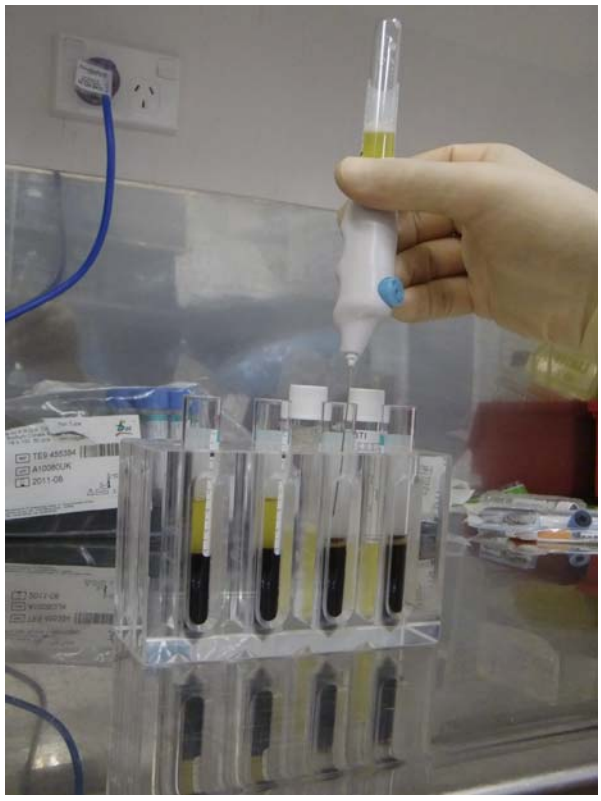

**FIGURE 1.** Represent the selected platelet-rich plasma (PRP) fraction a single spin centrifugation would yield using a 3.8% sodium citrate 9mL tube (PRGF technique, 580 g for 8 min) . The 2 tubes on the left side is now left with the PRGF layer above the white blood cells, which are not part of the final concentrate. The PRP from the 2 tubes on the right was already drawn by the pipette.

The main growth factors in the PRP concentrate are transforming growth factor β1 (TGFβ), platelet-derived growth factor, vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor 1. These biologically active growth factors work by stimulating angiogenesis, epithelialization, cell differentiation-replication-proliferation, and the formation of extracellular matrix and fibrovascular callus.[20–22]

Most of the published evidence of the effectiveness of PRP is formed from expert opinion[23,24] and only recently are articles being presented on the role of PRP in the shoulder region. We will next briefly discuss the key articles, which form the scientific basis for the use of PRP on acute injury, tendon rupture, and the chronic overuse states of tendinopathy.

At a microscopic level, injections of plasma rich in growth factors (PRGF) within Achilles tendon fascicles in sheep have lead to increased cell number and angiogenesis.[25,26] Similarly, there was increased angiogenesis on color doppler in surgically treated equine superficial digital flexor tendon lesions[27] after the application of PRP. Tenocyte stem cells became larger, were well spread, and elongated with the down regulation of nucleostemin expression after PRP application.[28]

In addition, histologic changes and improved biomechanical properties have been noted after the use of PRP. After percutaneous injections of PRP to the transected rat Achilles tendons, the tendon callus strength and stiffness was 30% higher after 1 week.[29] Increased tendon regeneration and strength have been reported in repaired tendons after only 1 injection at 1 week after surgery.[30] Lyras' group report faster healing of the PRP group compared with controls and histologically increased numbers of various cell types during the first 2 weeks of healing. There were varying responses of insulin-like growth factor 1 and TGFβ growth factors during the first 4 weeks.[31,32]

Although there are relatively few studies in human patients, patients with ruptured Achilles tendons have shown accelerated functional recovery with the addition of PRGF injections. The PRGF group also had decreased cross sectional area in the healed tendon after 18 months. We have conducted a level 1 study comparing percutaneous repair of the Achilles tendon biologically augmented with PRGF injections. Similar to Sanchez' group we have also utilized ultrasound for follow-up examinations showing improved healing characteristics at early stages but with reduced scar formation and more normal looking tissue in the treated group.[21]

There is increasing evidence of the role of PRP in the treatment of chronic tendinopathy. Gaweda et al[33] study reports significant improvement of outcome scores after the administration of PRP for patients with Achilles tendinopathy. Single PRP injections lead to 91% improvement in symptoms in a small series of 8 athletes with chronic patellar tendinosis. In addition, MRI images revealed a noticeable reduction in tendon irregularity of the affected tendon in 80% of the patients.[34]

Mishra and Pavelko[35] attempted a cohort study of the injection of PRP versus local anesthetic for chronic elbow tendinosis. Although patients reported an improvement in symptoms when PRP was administered (60% vs.16%) three fifths of the control group withdrew or sought other treatments preventing definitive long-term comparisons. When PRP was compared with corticosteroid injection for elbow lateral epicondylitis, patients receiving PRP had reduced pain and improved function.[36] Filardo et al[37,38] reported prospective case series on PRP administered to patella tendons for tendinopathy, reporting improved Tegner and visual analog scores.

The majority of physicians who commonly use PRP utilize a series of injections; however, De Vos[39] used only a single injection for treatment, in a prospective randomized study of 53 patients with Achilles tendinopathy. The mean validated Victorian Institute of Sports Assessment-Achilles questionnaire improved in both treatment (eccentric and PRP) and control (eccentric only) groups without significant improvement in the treatment group, suggesting that the single injection of PRP did not improve outcome. The fact that a single injection was given rather than a series of 3 injections means that this study may not be comparable with generalized practice.

Given the lower limb predisposition for tendinopathy, it is not surprising that there have been fewer studies on the upper limb pathology particularly the shoulder.

Samples of tissue have been analyzed for growth factors at the time of surgery for cuff repair. These have shown increased growth factors TGFβ compared with shoulders in the presence of instability.[40] The discovery of TGFβ and vascular endothelial growth factor in the bursa of other shoulder patients [41] and osteoinductive growth factors during ovine bone and soft tissue formation[42]

suggests that there may well be a role for the treatment of shoulder tendon pathology with PRP in the future.

As research progresses, the benefits of PRP and PRGF injections are being increasingly appreciated. The use of PRP should be considered to be experimental in all aspects of sports medicine.[43] The current lack of evidence is not a reason to withhold its use given the lack of recognized side effects.

## INDICATIONS FOR PRP APPLICATION IN TENDON HEALING

In general, there are 2 major indications where PRP is applied in tendon injuries. The most beneficial one, with the best expected results, would be acute tendon injury, whereas the other is the long standing tendinopathy. Unlike steroid injections which is known to predispose the soft tissue to future injury, damage, and possible tear, PRP does not seem to have any negative side effects. The fact that the treatment is being prepared from the patient's own blood, makes it a safe, easy, and reproducible treatment.

Only a few centers around the world have enough experience to claim expertise in PRP treatment. Even fewer centers have presented their experience with top-level athletes, claiming that PRP may reduce their return to play time.[13,44] High-level studies to confirm this belief are still awaited. Professional athletes will not participate in any study in which there is the possibility that they could actually not be given the treatment arm of a study or a placebo treatment. As a result, the evidenced-based medicine for PRP treatment in professional athletes lags behind the clinical impression obtained from recreational athletes and the nonsporting population. Only recently well designed scientific studies are beginning to form around this cohort of patients. The following indications have been used in published series of PRP treatment and represent the more common tendon pathologies treated by this technique. It should be emphasized that as long as an authorized, accepted, and safe technique is applied, this treatment can be performed for every tendon or muscle injury, regardless of its anatomic location.

The relatively short worldwide experience with acute tendon injuries treated by PRP needs to be reported. It is possible that the application of platelets, with their accompanying growth factors, is capable of speeding up the healing process, initiated after an injury.[45] The theory behind this encouraging clinical and laboratory results suggests that by applying PRP to the injured site, we advance over a phase of the natural healing process. When a tendon, or muscle, is injured we expect them to go through the 3 known stages of the healing process: inflammation\degeneration, regeneration, and fibrosis. It is usually the platelets, within the hematoma formed at the site of injury, which initiate this chemotactic cascade[46] and attracts growth factors, which will take over the process. PRP reduces the steps in the healing cascade and so yields better quality tissue in a shorter period.

PRP may be either applied during conservative treatment or during a repair procedure. As an adjuvant-conservative measure, PRP may be applicable for almost every musculotendinous junction injury in the body and to tendon midsubstance tears, acute or acute on chronic, provided the tendon ends are not retracted, for example partial thickness tears of the rotator cuff tendons, Achilles tendon, or peroneal and tibialis posterior tendons.

PRP is also being used during repair procedures. The treatment is applied intraoperatively at the end of surgical repair or reattachment. Alternatively, injections may be given after the initial hematoma has resolved or arthroscopic irrigation fluid has absorbed as an adjunct to surgery. Suitable upper limb examples include arthroscopic rotator cuff or finger flexor tendon repair. Additional injections should be timed at 3 to 5 days after surgery.

The clinical picture of chronic tendon injuries and tendinopathy is pain and swelling associated with a failed healing response and is an active tendon cell-mediated process. This involves increased turnover and remodeling, and gradual transformation in the quality and quantity of extracellular matrix that habitually precedes tendon rupture. Few researchers have studied the influence of PRP on this very "hard-to-treat" entity. As oppose to acute tendon injuries, which are usually "virgin in nature," the variety of scenarios and presentations here is endless as tendinopathy may present at any degree of severity and chronicity. Many of these patients have already been treated with a variety of methods and modalities before PRP treatment, and as result the patients are often chronic cases.

## PREPARATION AND APPLICATION

The process of PRP preparation is relatively straight forward and once practiced and mastered can be performed in the clinic or in the operating room, taking only a few minutes. The cost varies widely depending on the method used to produce the PRP. A commercial kit product might cost several hundreds of dollars, whereas inhouse manual fractions separation techniques produce a PRP concentrate for $< 20$ dollars. It is beyond the scope of this study to describe the differences between the different PRP preparation techniques. Recent study by Castillo et al[47] has confirmed that products from commercially available PRP separation systems produce differing concentrations of growth factors and white blood cells. Each and every PRP production technique involves the sterile aspiration of blood, these samples then undergo the centrifugation, either a single or double spin. Most of the commercially available PRP kits eliminate the need for manual separation as the final collecting vessel is a patent registered syringe for easy concentrate application. These kits will always contain leukocytes within the applied concentrate as gravity fractions separation after centrifugation cannot differentiate between the leukocytes and the lowest plasma layer known to be rich with growth factors. Accordingly, platelet concentrates have been categorized into pure PRP, in which leukocytes are purposely eliminated from the PRP (as with the manual technique), and leukocyte and platelet-rich plasma (L-PRP), containing also high concentration of leukocytes. The improved homogeneity of pure PRP and its reduced donor-to-donor variability would support the view that some PRP production techniques are more reproducible and predictable than others.

In addition to the variation in quality and composition there are frequently variations in the methods of administration. These methods include the form of application; liquid or matrix, the timing of treatment and injections, the number of injections per series or volume of injection. Each method generates product of varying biological properties and varying uses. These variations prevent the development of a standard dose of PRP, and thus hamper the collation of scientific evidence of its effects. It is unclear whether

these differences have any clinical relevance. To add into the discussion, the actual growth factor content does not correlate with the platelet count in whole blood or in PRP when leukocytes are present in the preparation, and there is no evidence that sex or age affects platelet count or growth factor concentrations.

After appropriate clinical examination and suggested diagnosis, imaging will assist in establishing the exact location and extent of the injury. As PRP is considered to best act when placed at the site of injured tissue, we recommend ultrasound guidance to verify accurate needle placement, for example for nonoperatively managed partial rotator cuff tears (Fig. 2). It may be assumed that application bathing the concentrate around and over the injured tendon would be sufficient for absorption into the healing area preventing separation of healing layers of tendon fibrils. We recommend that exudates, hematoma, or reactive inflammation around the tendon, is removed by aspiration before PRP is injected.

The concomitant use of local anesthesia with the application of PRP may be disadvantageous. Many surgeons believe that the concomitant use of local anesthetic and PRP will be detrimental to the final clinical outcome. This is thought to be due to pH tissue changes and the biological activity of the PRP concentrate and the surrounding environment. We, therefore, recommend avoiding local anesthetic when injecting PRP into a relatively superficial tissue, until scientific evidence affirms or refutes its use. Local anesthetic infiltration of the skin and the immediately subcutaneous tissue will assist needle placement towards deep target tissues, for example the rotator cuff.

When PRP is administered at arthroscopy, the injection should be performed after draining the joint or the subacromial space of irrigation fluid (Fig. 3). Precise intra-articular application can be performed for meniscal repair and glenoid labrum restabilization by leaving the needle in the designated location just before performing the above. In the case of open or mini open surgery, PRP can be applied as a gel just before closure or by infiltrating the concentrate over the desired area. Solid matrices can also be sutured or glued to the desired location, for example over a rotator cuff repair. The application of PRP mesh has the benefit of ease

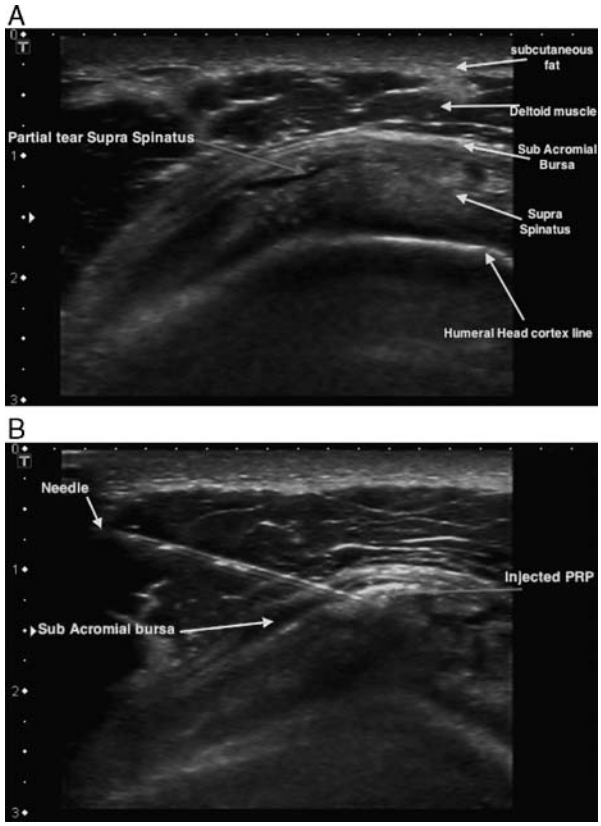


**FIGURE 2.** A, An axial ultrasound (US) picture of a supra spinatus partial tear (red arrow). Orange arrows are pointing at the anatomic landmarks of the region. The hypoechoic/black appearance of the tendons and muscles, especially in the left side periphery of the pictures is the result of the anisotropic phenomena, an US artifact, and a good example why US is very operator dependent. B, An axial US picture of a supra spinatus partial tear during its injection with PRP, seen as the white/hyperechoic area marked with red arrow. The PRP is now filling the tear within the tendon and starts to spread out into the subacromial to subdeltoid bursa along its plane, covering the supra spinatus.

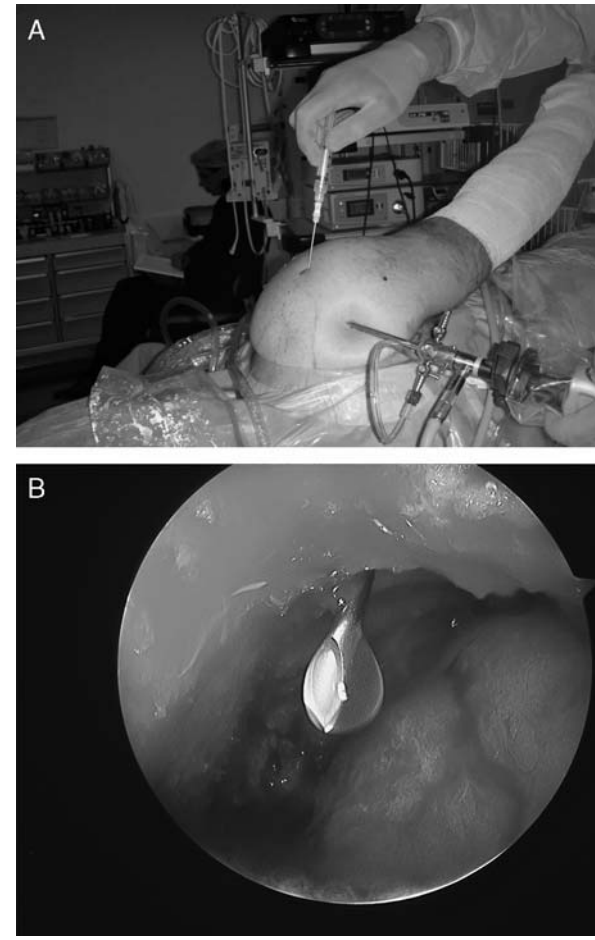


**FIGURE 3.** A and B, Arthroscopic rotator cuff repair, followed by PRGF injection over the repaired tendon through the subacromial joint. When PRP is administered at arthroscopy, the injection should be performed after emptying the joint of arthroscopic fluid. Once surgical procedure is complete, the appropriately placed needle can infiltrate the target tissues or spread around the repaired site, under dry vision as seen on the liquid crystal display (LCD).

of use but the timing of application is such that the initial release of growth factors may be missed during the coagulation process. This may be minimized by preparing 2 separate serum samples. The first may be allowed to coagulate and form the fibrin matrix. The second can be activated at a later stage and injected into this matrix to supplement the healing process. A combination of both techniques may be used to provide local infiltration of the repair site with growth factors and the repair may then be covered with the growth factor enriched fibrin matrix.

The area to be injected should be prepared in a sterile manner, similar to lumbar puncture procedure. Superficial tissues can be reached using a 23 G (blue) hypodermic needle and a 18 G (pink) spinal needle (blue) for deep soft tissue injections. When injecting a deep joint, for example the hip, we sometimes prefer to use the 22 G (black) spinal needle (BD) if local anesthesia is not used. For rotator cuff injection a 23 G needle is sufficient for most patients; however, very muscular athlete might require a longer spinal needle.

For safety reasons we recommend the use of a Luer lock syringe. This prevents separation of the needle from the syringe due to the pressure applied. Pressurized detachment is clearly dangerous as it can cause hazardous spraying of biological material with inoculation risks and wasteful with the loss of the precious PRP. We also recommend injecting the PRP in an easy and slow manner to avoid needle misplacement. Ultrasound guidance allows continuous precise localization of the injection.

## POSTOPERATIVE MANAGEMENT

Platelets influence the early phases of regeneration and healing process, but this allows mechanical stimulation to start driving neotendon development at an earlier time point, which shown to keep it constantly ahead of controls.[30] However, PRPs should be combined with an appropriate regimen to enhance extracellular matrix organization in the short term. Injections of PRP 1 week postoperatively increased tendon regenerate strength after 4 weeks if combined with early therapy.[48] Recently, a placebo-controlled experimental trial in 6 horses reported less inflammation and increased metabolic activity and maturation, higher strength at failure and elastic modulus in tendons treated with PRP.[27] In Achilles tendon repair, those patients who had received PRP recovered normal range mobility after 7 weeks rather than 11 weeks and were able to return to play earlier at 14 weeks compared with 22 weeks for the control group.[21]

Other studies show similarly improved early discharge from hospital after total knee replacement. Berghoff et al[49] performed a randomized prospective study for the application of autologous platelet gel during closure of total knee arthroplasty. Treated patients also had an improved range of motion at 6 week. Improved range of motion at 6 weeks postoperatively has also been noted by others investigators administering platelet gel during total knee replacement.[50]

In light of the improved outcomes with the addition of PRP, many clinicians utilizing PRP in their practice would speed up the standard and common rehabilitation process. This is clearly advantageous to professional athletes who wish to return to play time in as short a time as possible. Most of the published literature of accelerated return to playwith professional athletes, is anecdotal and prospective studies are only currently at the design and initial phase. We recently published a case report of an Olympic judoka, which had completely ruptured his elbow medial complex (both medial collateral ligament and common flexor tendon origin) just 10 months before his goal competition, the Olympic Games. Surgery at that stage would have ruled out competition within the next 6 to 8 months and miss Olympic qualification. He decided upon a conservative management plan involving PRGF injections together with an accelerated rehabilitation protocol. He received 2 injections during recovery, at 1 and 2 weeks after sustaining the trauma, and by 6 weeks from injury his elbow had stabilized. He went on to win a gold medal in a world cup tournament, five and a half months past his injury.[51]

It is worth noting that given the lack of definite current evidence for the benefits of growth factors to promote healing and strengthening of the tissue formed, some sports physicians believe that rehabilitation regimes should remain unaltered.[52,53]

So far PRP has been administered mainly during the inflammatory and proliferative stages of healing, typically during the first 6 weeks after surgery. Currently, literature reports only studies in which PRP is applied during the surgical procedure itself. It is logical to assume that PRP injections further down the healing pathway after rotator cuff repair will have an additional beneficial effect on the recovery process. We are currently studying this hypothesis, in a level 1 manner, and expect results later in the year.

After a rotator cuff repair, the limb may either be protected or have a moderate restriction depending on the size of the repair and the repaired tissue quality. Given a program of criterion-based progression consisting initially on the quality of the repaired tissue, the degree of pain, range of motion, end feel, quality of range of motion neuromuscular control, proprioception, and strength it is likely that patients will recover rapidly. A typical rehabilitation timetable is likely to be as follows:

| | Grade 1 Tear | Grade 2 Tear | Grade 3 Tear |
|---|---|---|---|
| Protection | 0-2 wk | 0-3 wk | 0-4 wk |
| Passive ROM exercises | 2-4 wk | 3-6 wk | 4-8 wk |
| Flexion exercises | 4-8 wk | 6-12 wk | 8-16 wk |
| Strengthening exercises | 8-12 wk | 12-16 wk | 16-24 wk |
| Global resistance exercises | 12-16 wk | 16 wk | 24 wk |

The grading system for the above table was adopted from Dr Mat Brick (of "The millennium institute of sports and health," Auckland, NZ) and follow a very simple and logical concept. Grade 1 stand for a small tear with good quality repaired tissue, grade 2 is larger tear with good tissue or small tear with poor tissue, and grade 3 would then stand for larger tear with poor tissue require maximal protection.

Care should be taken with the provision of postoperative analgesia. The majority of patients use a combination of analgesics and anti-inflammatory medication. It seems illogical to introduce growth factors from platelets to promote healing and yet concurrently administer anti-inflammatory medication which have their mechanism of action by inhibiting platelet function. Although there is published data on the role of non steroidal anti inflammatory drugs and the healing of various tissue such as bone, tendon, and muscle, there are no data on concomitant use with PRP. We, therefore, recommend to avoid non steroidal

 

anti inflammatory drugs, when possible, at least 2 days before PRP application and throughout the treatment time frame, usually up to 2 weeks after treatment.

## DISCUSSION

There have been several articles published on human patients reporting on the outcome after surgery with the addition of PRP. Procedures reported include treatment for subacromial bursitis and impingement, open subacromial decompression, and rotator cuff surgery.[54,55]

Jimenez-Martin et al[56] reported an improved pain score and reduced rehabilitation time when PRP was used in a retrospective cohort comparison and was applied to traditional, mini open, and arthroscopic subacromial surgery. The exogenous application of platelet leukocyte gel during open subacromial decompression was thought to contribute to faster recovery, earlier return to daily activities, and less analgesic requirement.[57]

PRP was used to augment arthroscopic cuff repair in a case series of 14 patients leading to improved pain and functional outcome without any adverse events.[55] Randelli et al[58] have recently followed this case series with a level 1 prospective randomized double-blind controlled study for augmented arthroscopic cuff repair. Patients reported significantly less pain and improved strength in external rotation and functional Simple Shoulder Test, UCLA, and Constant scores at 3 months after surgery. No difference was shown in scores between the 2 groups at 6, 12, and 24 months after surgery. Imaging also did not show a difference. For smaller tears (grades 1 and 2) with less retraction there was significantly higher external strength at all stages.

Recent work by Castricini et al[59] report a level 1 study comparing the use of an autologous platelet-rich fibrin matrix for the treatment of rotator cuff tears. There was no significant difference in Constant scores in small and medium-sized tears; however, the investigators comment that other preparations of PRP may be effective and that PRP may be beneficial in large and massive rotator cuff tears.

As research progresses, the benefits of PRP and PRGF injections are being increasingly appreciated. Although there is currently a lack of evidence to give firm treatment recommendations for the use of PRP in rotator cuff surgery, the absence of reported side effects means that its use is safe and seemingly without risk. The current lack of evidence is not a reason to withhold its use. The use of PRP should be considered to be experimental in all aspects of sports medicine.[43] We encourage randomized prospective studies using a standardized form of PRP so that outcomes can be measured and firm conclusions can be made.

### Summary

The use of PRP has shown to improve healing when compared with standard healing times; however, there is currently a lack of prospective randomized studies in the literature. It is logical to assume that PRP injections after surgery will have a beneficial effect on the ongoing healing process of rotator cuff repairs and there have been no complications reported from its use. We recommend that PRP be used for treatment in randomized prospective controlled studies so that firm conclusions can be made.

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