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Platelet-rich plasma for the treatment of partial rotator cuff tears

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Thesis

**PLATELET-RICH PLASMA FOR THE TREATMENT OF PARTIAL ROTATOR
CUFF TEARS**

by

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DEDICATION

To Fr. James Coughlin SJ, for setting in the wheels in motion that prompted me
to study science and pursue medicine as a career.

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Finally, I'd like to thank my parents and sister for their continuous support and love, without which none of this would be possible.

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CUFF TEARS**

ANTONIO LOCCISANO

ABSTRACT

Rotator cuff tears are a common injury impacting a large and diverse group of patients and refer to a partial or full discontinuation of one or more of the muscles or tendons comprising the shoulder complex. It may occur as a result of traumatic injury, applied weight, overuse, or intrinsic degeneration over a period of years. The incidence of rotator cuff tears has been found to increase with age. Though not a life-threatening condition, rotator cuff tears adversely affect the quality of one's lifestyle causing significant pain, weakness, and limitation of motion that hinders a person from performing routine daily activities as adequately and frequently as desired.

Data from cadaveric studies suggest that as many as 65% of individuals over the age of 70 have a partial-thickness rotator cuff tear. Oftentimes, rotator cuff tears are asymptomatic which can make diagnosis and early treatment challenging. The decision to pursue operative versus conservative management is often controversial. Though surgical intervention may provide more immediate pain relief and functional improvement, it portends a higher risk of morbidity than conservative measures, particularly with an older demographic of patients. Moreover, surgical repair is often followed by long recovery periods and has variable outcomes. A number of conservative treatment options are currently

being utilized for the management of partial rotator cuff tears including oral medication, corticosteroid injection, and targeted physical therapy.

This review seeks to assess an innovative, biologic approach to treating partial rotator cuff tears using autologous platelet-rich plasma (PRP). The use of PRP for the conservative management of both degenerative and acutely injured tissues is quickly becoming a more popular option within the clinical community. PRP treatment has received significant attention from the media and has been used by several professional athletes as a means of expediting the healing process. The appeal of PRP stems from the fact that it is produced from a patient's own blood. After a blood sample is obtained, it is placed into a centrifuge, a tool used to separate the blood into its many components. A large concentration of platelet-enriched plasma can then be collected and augmented before administration to an injured area of bone or soft tissue, such as a tendon or ligament. Platelets contain an abundance of growth factors essential for cellular recruitment, proliferation, and specialization required for the healing process. PRP is given to a patient via an injection, often under ultrasound assistance for more precise placement.

This study reviewed a collection of current literature on the efficacy of PRP in rotator cuff repair. Published studies have generally illustrated a general trend towards effectiveness, suggesting PRP may improve patient outcomes and prevent the need for surgery in patients with partial rotator cuff tears. Study designs and results have proved to be inconsistent at times. However, further clinical investigation is required to validate the use of PRP as an additional non-surgical treatment option.

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LIST OF ABBREVIATIONS

ASES	American Shoulder and Elbow Surgeons
bFGF	Basic Fibroblast Growth Factor
CTGF	Connective Tissue Growth Factor
DASH	Disabilities of the Arm, Shoulder, and Hand
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor
FBS	Fetal Bovine Serum
FT RCT	Full-thickness Rotator Cuff Tear
GAG	Glycosaminoglycan
GF	Growth Factor
HGF	Hepatocyte Growth Factor
IGF-1	Insulin-like Growth Factor-1
MRI	Magnetic Resonance imaging
NSAID	Non-Steroidal Anti-Inflammatory Drug
PDGF- β	Platelet-Derived Growth Factor-Beta
PCR	Polymerase Chain Reaction
PPP	Platelet-Poor Plasma
PRGF	Platelet-Released Growth Factor
PRP	Platelet-Rich Plasma

PT	Physical Therapy
PT RCT	Partial-Thickness Rotator Cuff Tear
RCTs	Rotator Cuff Tears
SER	Strength in External Rotation
SPADI	Shoulder Pain and Disability Index
SST	Simple Shoulder Test
TG	Transglutaminase
TGF- β	Transforming Growth Factor-beta
UCLA	University of California, Los Angeles
VAS	Visual Analogue Score
VEGF	Vascular Endothelial Growth Factor

INTRODUCTION

Rotator cuff tears (RCTs) are a common injury among a diverse group of patients, with prevalence of injury increasing linearly with age [52]. It is a condition typically characterized by weakness and pain in the shoulder that is aggravated by overuse, applied weight, raising/lowering or rotating the involved arm, as well as overhead physical activities such as tennis, baseball, and swimming [45]. The supraspinatus muscle and tendon are the most common sites of injury and can be damaged by both traumatic injuries and degenerative changes [15].

Data from cadaveric studies suggest that as many as 65% of individuals over the age of 70 years have a partial-thickness rotator cuff tear [34]. Oftentimes, rotator cuff tears are asymptomatic, which can make diagnosis and early treatment challenging [25, 52]. The decision to pursue operative versus non-operative management is therefore often controversial. Surgical management may provide more immediate pain relief and functional improvement, but it portends a higher risk of morbidity than conservative measures, particularly with an older population of patients [31]. Moreover, surgical repair is often followed by a long recovery period and has variable outcomes [31]. Current conservative treatments of partial rotator cuff tears include activity modification, oral medication, corticosteroid injection, and/or

targeted physical therapy [28, 52]. Improperly managed partial rotator cuff tears can progress to debilitating full-thickness tears if left untreated [31].

This review seeks to assess an innovative, biological approach to treating RCTs using autologous platelet-rich plasma (PRP), with the goal of distilling a safe and readily available, long-lasting treatment option that can be offered to a wide range of patients. The use of platelet-rich plasma for the conservative management of both degenerative and acutely injured tissues is gaining recognition and popularity in the international community of clinician-scientists. A large retrospective review on the use of ultrasound-guided PRP injections for chronic tendinopathy in various bodily regions reported an 82% improvement in symptoms across all surveyed patients [31]. Furthermore, experiential clinical data suggests that PRP is often an effective treatment for partial rotator cuff tears. Still, supportive data from published literature remains limited and is of variable quality and consistency.

This paper will first provide relevant background information on the anatomical function of the shoulder complex, with an emphasis on the rotator cuff and its pathophysiology, and next explore some of the most currently utilized therapeutic interventions. The use of PRP as an innovative biologic augmentation of rotator cuff repair will then be introduced, and various proposed studies involving the use of PRP as an alternative treatment option will be discussed, leading to an analysis of patient outcomes and a critique of each study's value. By evaluating the therapeutic value of PRP, this review can

potentially validate an additional non-surgical alternative for the treatment of partial RCTs and contribute to identifying specific sub-groups of patients and pathologies that would gain the great benefit from its use in future studies.

Functional Anatomy of the Shoulder Complex

The shoulder complex is composed of a number of interconnected bones, joints, and a specialized set of soft tissues including muscles, tendons, and ligaments that are designed to stabilize the arm and provide optimal mobility to the upper extremity. The bony structure of the shoulder complex is primarily composed of the humerus (i.e. upper arm bone), the scapula (i.e. shoulder blade), and the clavicle (i.e. collarbone) [12]. The clavicle is the most complex bone of the three and is composed of a body and three bony extensions: the glenoid, the coracoid, and the acromion [15]. The four joints of the shoulder, named according to the bone processes they connect, include the glenohumeral, acromioclavicular, sternoclavicular, and scapulothoracic [12, 15].

The glenohumeral joint (Figure 1) is a ball and socket joint that is capable of a wider range of motion than any other joint in the body [12, 15]. The rounded, ball-shaped head of the humerus is seated in the socket-shaped glenoid cavity of the scapula. Because of its increased mobility, the glenohumeral joint is also the least stable joint, relying on other components for its maintenance [12, 15]. The glenoid cavity covers only a portion of the humeral head and the fibrocartilaginous labrum deepens the relatively shallow socket, helping to keep

the humeral head in place. A joint capsule enveloping the glenohumeral joint is lined by a synovial membrane that secretes fluid to help lubricate, absorb shock, and nourish the joint [12, 15]

The sternoclavicular and acromioclavicular joints work together to suspend and stabilize the shoulder girdle as well as contribute to increase glenohumeral mobility. Rotation at the acromioclavicular joint and elevation at the sternoclavicular joint allow for complete elevation of the arm [15]. The scapulothoracic joint represents the articulation connecting the scapula to the posterior part of the thorax and is responsible for maintaining the full range of motion of the scapula. Scapular motion is essential for overall shoulder mobility with a 1:2 degree ratio of motion between the scapulothoracic and glenohumeral joints [15].

Unlike the hip, which is also a ball and socket joint but with a deeper socket for stability, the shoulder is constructed for motion more so than stability [2, 44]. The humeral ball of the shoulder joint is therefore reliant on the soft tissues both for its stability and motion [2, 44]. The rotator cuff consists of four muscles and their tendons that connect the humerus to the scapula and provides stability to the shoulder while allowing it to rotate [2, 44]. It is formed by attachment to the joint capsule of the supraspinatus muscle anteriorly, the infraspinatus and teres minor posteriorly, and the subscapularis muscle anteriorly (Figures 2 & 3) [2, 44].

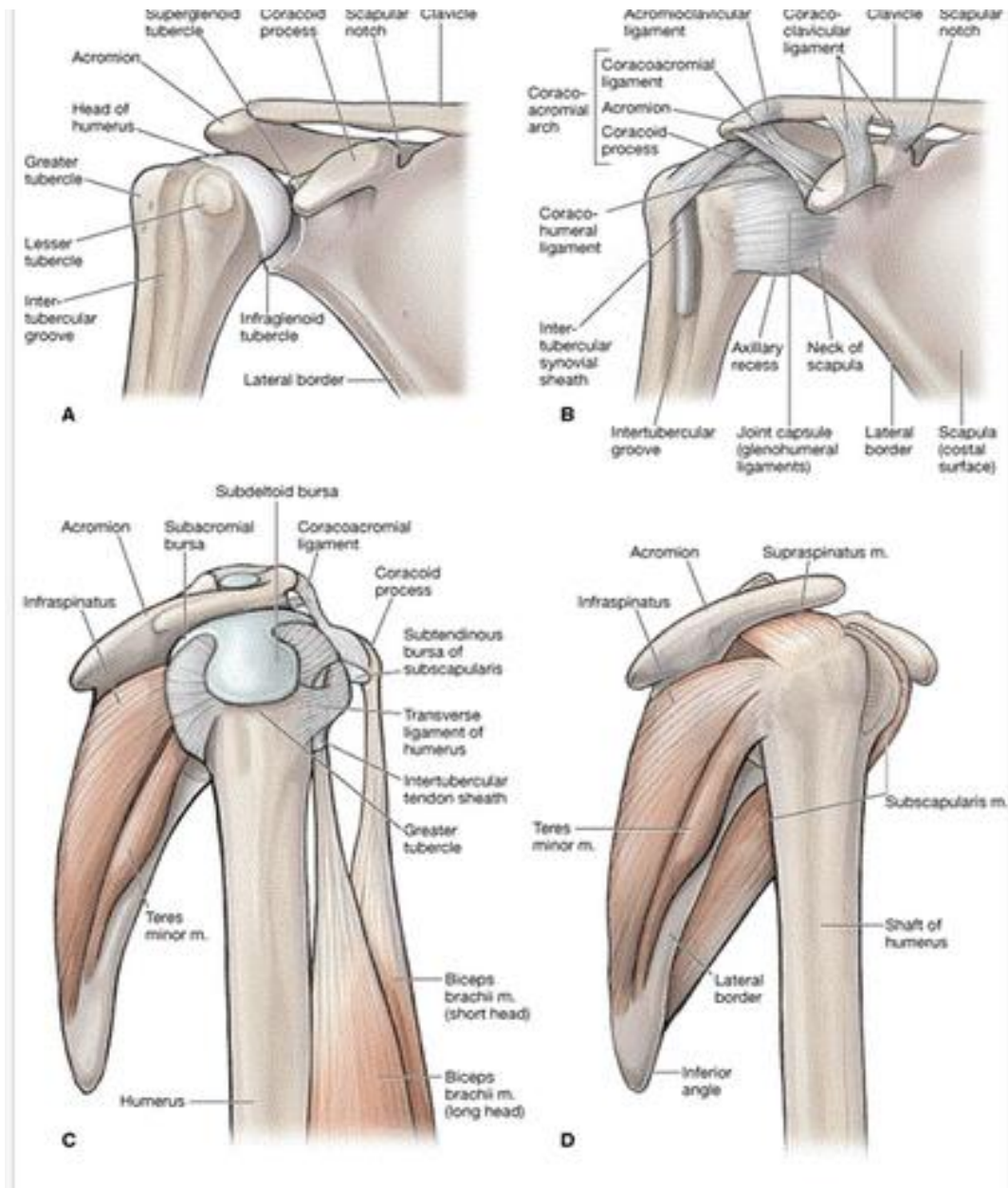


Figure 1. Glenohumeral Joint and Rotator Cuff of the Shoulder Complex: This four-panel figure illustrates the glenohumeral joint of the shoulder from an anterior view (A) and the accompanying joint capsule (B), as well as the rotator cuff of the shoulder with the associated bursae visible (C) and from a lateral view (D).

Source: Morton, D.A., Foreman, K.B., & Albertine, K.H. *The Big Picture: Gross Anatomy*

Figure downloaded from <http://www.accessmedicine.com>

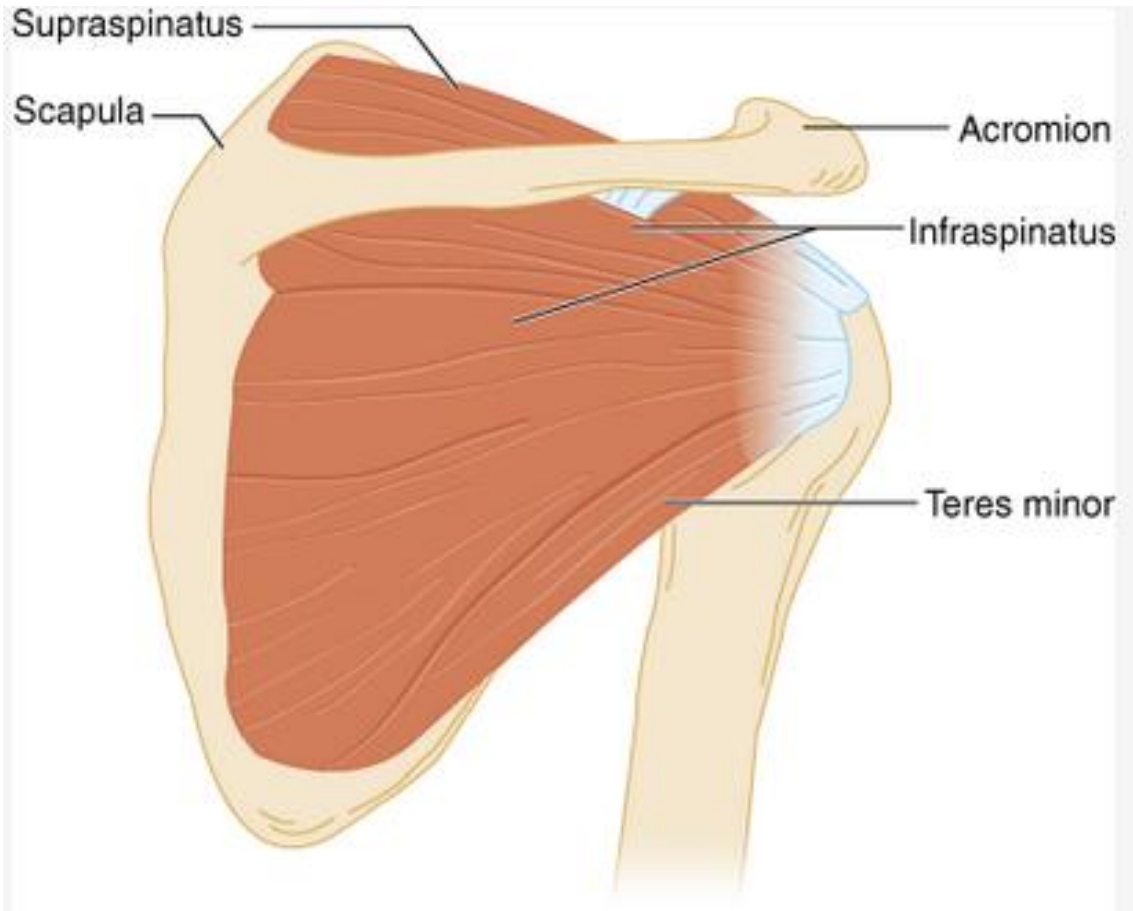


Figure 2. Posterior view of the Shoulder Complex with Rotator Cuff

Muscles: This figure illustrates rotator cuff muscles originating on the posterior side of the shoulder: the supraspinatus, infraspinatus, and teres minor. The supraspinatus muscle attaches to the greater tuberosity of the humeral head by passing underneath the acromion, the bony process of the scapula. It is responsible for initiating arm elevation and for abduction of the shoulder. The infraspinatus also attaches to the greater tuberosity of the humeral head and is responsible for external arm rotation. The teres minor works with the infraspinatus to provide external rotation.

Source: Tintinalli, J.E., Stapczynski, J.S., Ma, O.J., et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th Edition.

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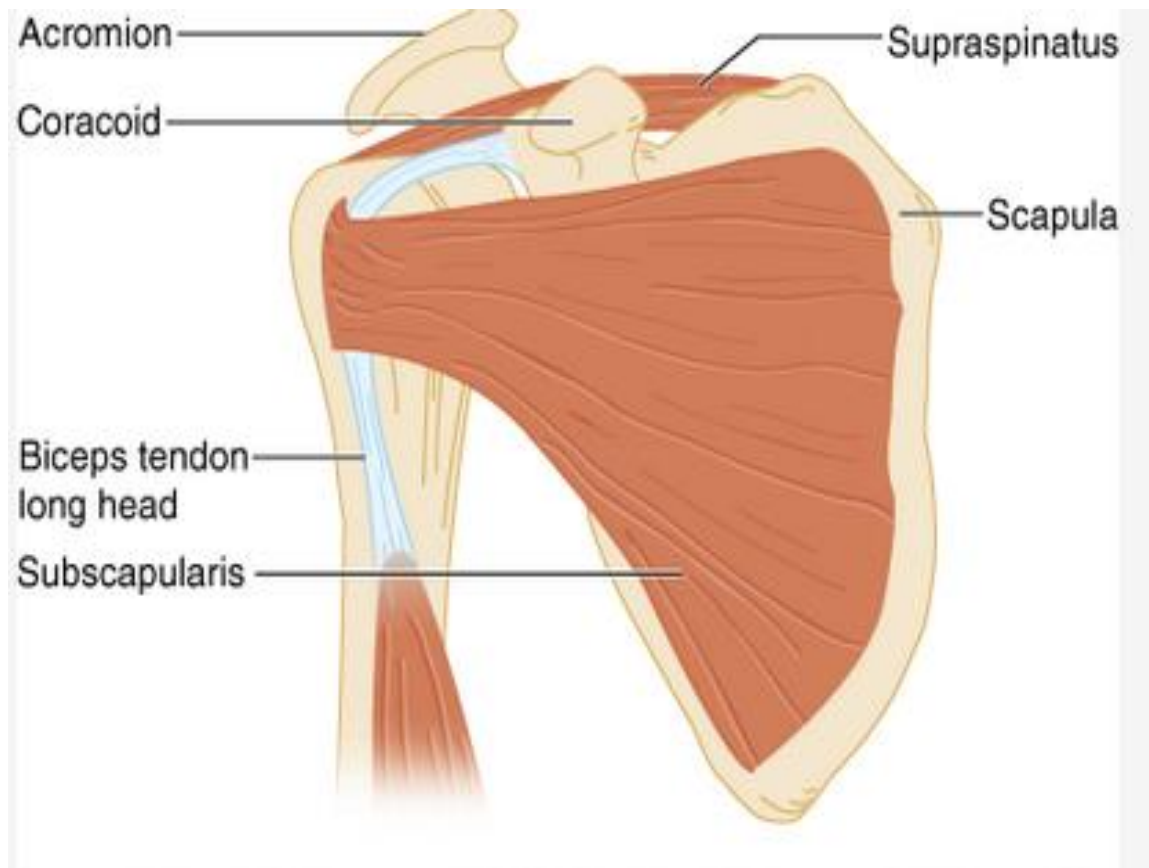


Figure 3: Anterior View of Shoulder Complex with Rotator Cuff Muscles:

This figure details the rotator cuff muscle originating on the anterior aspect of the shoulder. The subscapularis muscle is the only rotator cuff muscle that arises from the anterior aspect of the scapula. It attaches to the lesser tuberosity of the humeral head and provides internal rotation of the arm. Also illustrated is the long head of the biceps as well as the acromion and coracoid, two of the bony processes of the scapula.

Source: Tintinalli, J.E., Stapczynski, J.S., Ma, O.J., et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th Edition.

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Pathophysiology

Though the shoulder complex allows for the greatest range of motion in the arm, increased mobility comes at a price, often leading to instability or impingement of the soft tissue or bony structures of the shoulder and consequent pain [2]. Rotator cuff tears refer to structural failure and/or tissue disruption in any of the four distinct muscles and tendons comprising the rotator cuff [2, 15]. A tear causing rotator cuff disruption that does not extend all the way through the tendon is termed a partial-thickness rotator cuff tear (PT RCT). PT RCTs are more prevalent than full-thickness tears and do not lead to retraction of the muscle-tendon unit [10]. A tear that involves complete discontinuation of rotator cuff fibers is termed a full-thickness tear (FT RCT), resulting in contact between the articular and bursal spaces [10].

RCTs are one of the most common shoulder problems among a diverse group of patients, with the incidence increasing linearly with an aging population [23]. Data from cadaveric studies suggest that as many as 65% of individuals over the age of 70 have a PT RCT and as many as 28% of individuals over the age of 60 have had a FT RCT [52]. Oftentimes, RCTs are asymptomatic, making diagnosis and early treatment challenging [25]. Studies have shown that the size of a tear could be an important factor in the development of symptoms, and that it seems to be a trend toward a correlation between tear size, progression, and the development of new symptoms [52].

Injuries to the rotator cuff are multifactorial, causing irritation or damage to the muscles and tendons. Many theories over time have been proposed to explain the etiology of RCTs, which have been categorized into both extrinsic and intrinsic factors [52]. The chronic impingement theory first proposed by Neer is one of the best-known extrinsic pathologic factors in RCTs [52]. Impingement is one of the most frequent causes of shoulder pain in the general population, particularly in men and women who remain physically active in their thirties and forties [43]. Impingement refers to the mechanical compression and possible abrasion of the rotator cuff tendons and serves as a precursor to RCTs if the condition progresses (Figure 4). The most common site for an impingement is the supraspinatus tendon and is brought on by repetitive overhead use or movement of the shoulder above the horizontal plane [15]. This pinching can cause inflammation that continues to damage the tendon with repetitive motions and may involve thickening of the tendon [43]. Swelling within muscle tissue decreases its vascularity, causing the muscle to fray [43].

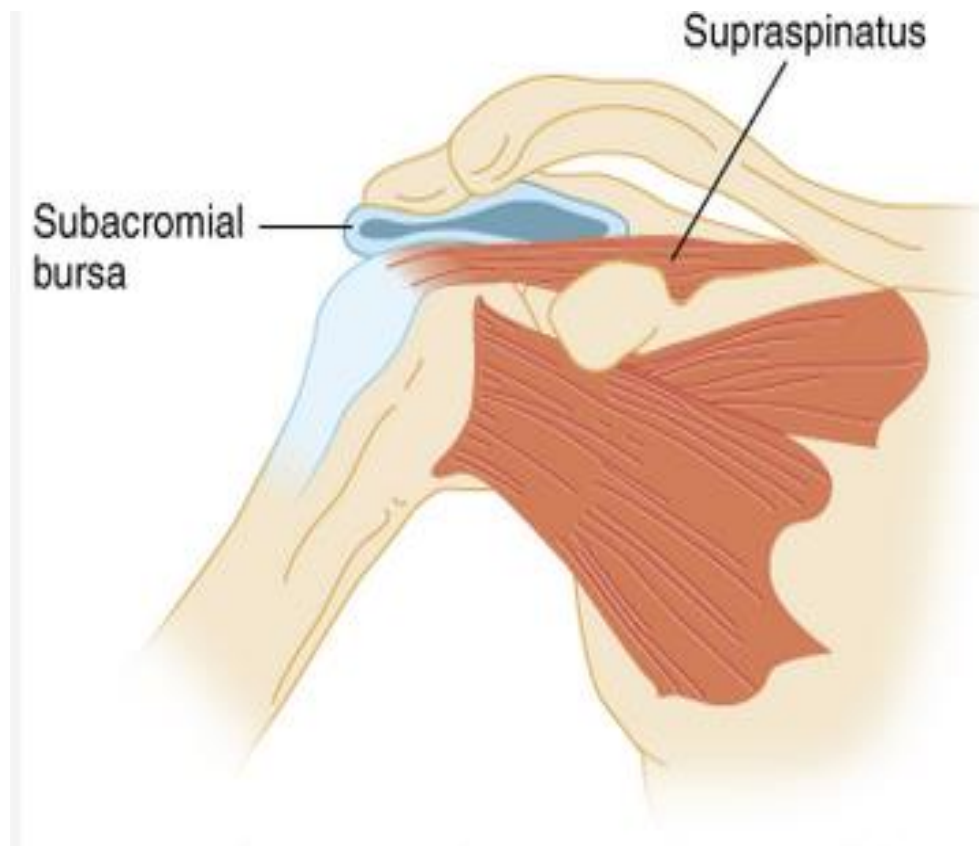


Figure 4. Impingement of the Subacromial Bursa and Rotator Cuff: This figure illustrates the mechanical compression and potential abrasion of rotator cuff muscles. When a person lifts his/her arm above the head, the supraspinatus and subacromial bursa may become pinched between the acromion and coracoacromial arch and the greater tuberosity of the humerus. This pinching can cause inflammation that continues to damage the tendon with repetitive motions and may involve thickening of the tendon.

Source: Tintinalli, J.E., Stapczynski, J.S., Ma, O.J., et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th Edition.

Figure downloaded from <http://www.accessmedicine.com>

Other important extrinsic factors include mechanical overuse of the shoulder, dislocations, and fractures of the greater tuberosity of the humeral head [49]. Factors that impede the natural healing process of tissues healing may also contribute to RTCs. Studies have shown that nicotine, for example, has a deleterious effect on tendon healing [16, 52]. Smokers are less likely to respond favorably to rotator cuff repair operations, with reduced post-operative function and satisfaction compared to nonsmokers [16]. Diabetes is another potential risk factor for RCTs [52]. In a study on patients with asymptomatic rotator cuff disease, it was found that histologic rotator cuff tendon changes related to age are more common in diabetics and that diabetic patients demonstrated a more restricted shoulder range of motion, higher incidence in re-tear rates after surgical repair, and higher rates of complications and infections after repair [52].

Clinical evidence suggests that most RCTs are caused by intrinsic factors such as microtrauma or degeneration [34]. Rotator cuffs may be torn from a single traumatic injury or, more commonly, from overuse of the muscles and tendons over a prolonged period of time that leads to the intrinsic degeneration of a tendon and eventual tear [34, 35]. The frequency and distribution of these degenerations suggest that they are common changes involved in the early degeneration of rotator cuff tendons before tearing occurs [52].

Studies conducted by Riley et al. in 2002 also point to extracellular matrix (ECM) modifications as another important intrinsic factor in the etiology of RCTs

[52]. ECM is the substrate to which cells adhere, migrate, and differentiate. It imparts information to cells and tissues by providing cell-binding motifs in its own proteins or by presenting growth factors (GFs) to the cells [52]. Physiologic and pathologic modifications to the ECM seem to be the most important intrinsic factors involved in tendinopathies and tendon ruptures. Transglutaminases (TGs) have found to be tied to the formation of hard tissue development, matrix maturation, and mineralization [52]. They are important in maintaining the structural integrity of tendons thanks to their crosslinking function under normal conditions [52]. Injured supraspinatus tendons have demonstrated a reduction in TG2 protein expression, one of nine different TGs found in mammals, and the fall of TG2 may mean the exhaustion of the tendon's capability to repair [52].

Diagnosis of Rotator Cuff Tears

Diagnosis of rotator cuff injury is made through the careful collection of a patient's medical history and physical examination. Practically speaking, it can be very difficult to distinguish between a FT RCT and PT RCT, or even between rotator cuff injuries from some other inflammatory rotator cuff condition in this manner [15]. The diagnosis is primarily clinically based on the finding of rotator cuff weakness upon examination of a patient with a history of chronic shoulder pain or acute shoulder pain after significant trauma [15, 25]. Routine shoulder radiographs are useful tools to evaluate RCTs and associated intra-articular

pathology, with magnetic resonance imaging (MRI) and ultrasound being two of the most common techniques used [48].

Ultrasound has proven to be a very valuable tool for diagnosing rotator cuff disease, particularly full-thickness RCTs [55]. It is capable of effectively evaluating patients with shoulder instability and postoperative patients with metallic artifacts that would otherwise obscure MRI findings. However, the ultrasound technique is significantly dependent on an experienced operator and appropriate equipment for the most accurate readings and is thus less practical in clinical settings [55]. Conventional MRI, on the other hand, is an extremely useful imaging modality in the evaluation of patients with shoulder pain (Figure 5). Studies have found MRI to have a sensitivity of 100% and specificity of 95% for diagnosing FT RCTs, as well as a sensitivity of 82% and a specificity of 85% for PT RCTs [55].

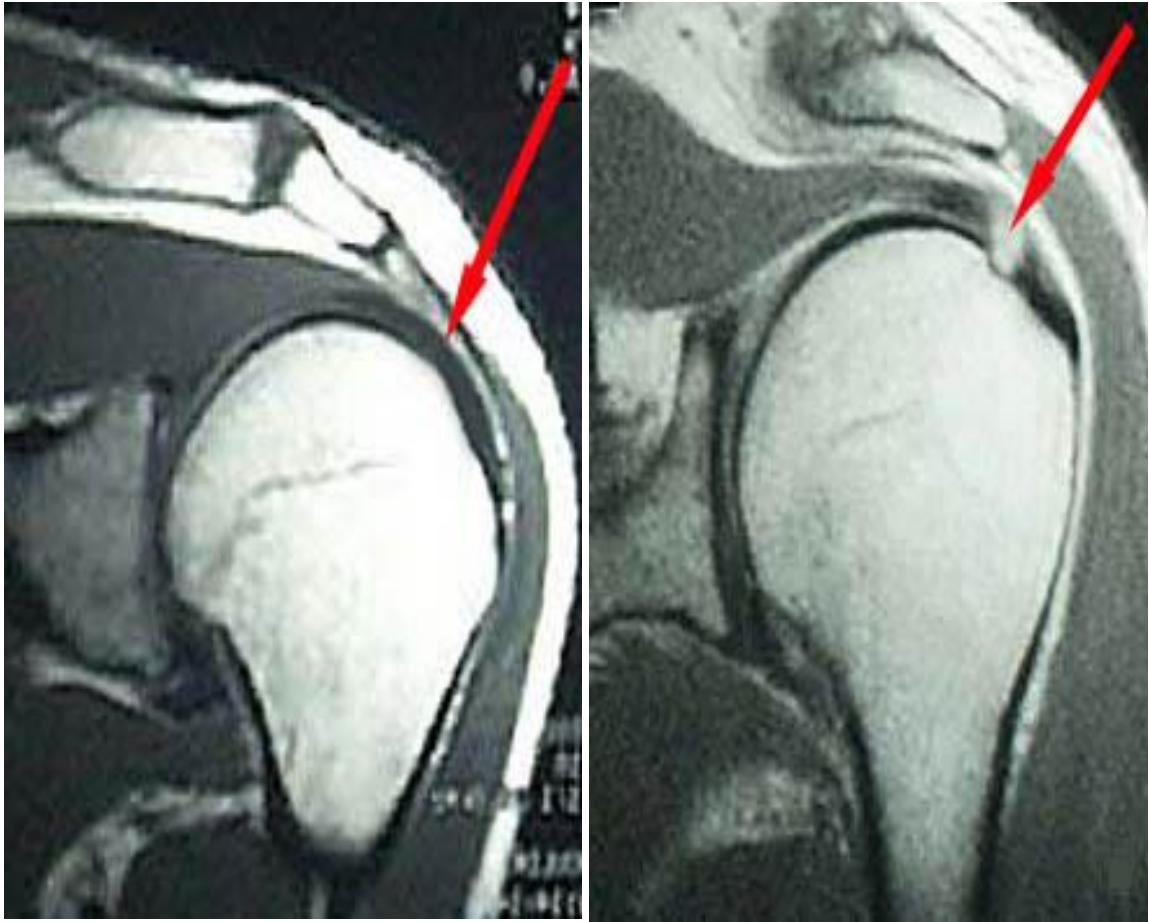


Figure 5. MRI Scans of Normal and Torn Rotator Cuffs: The figures illustrate the radiographic difference of a normal rotator cuff (left) as compared with a torn rotator cuff (right). Whereas the image of the normal rotator cuff displays a purely black signal band, denoted below the tip of the red arrow, the black band on the right is interrupted by a white signal, indicating a tear in the rotator cuff fibers.

Source: Mishra, A. MRI Scans of Normal and Torn Rotator Cuffs
Figure downloaded from <http://www.EMEDX.com>

Treatment Options

The decision to pursue operative versus non-operative management of rotator cuff tears is often controversial. To date, no definitive consensus exists as to what is the best management for patients, and new therapeutic options are

continuously being assessed and validated for their efficacy, often with contrasting results [28]. The published success rate of non-operative management varies widely, ranging from 33%-92%. Although current evidence is not sufficient to reach clear indications for conservative management of RCTs, several authors recommend non-operative treatment for patients experiencing pain without any dramatic or progressive signs of weakness [28]. Positive correlations have also been found with a number of prognostic factors such as clinical presentation, duration of symptoms, and tear size. Symptom duration lasting less than one year and tear size less than 1 cm, for instance, are good predictors of beneficial results with conservative treatment [28].

Surgical management may provide more immediate pain relief and functional improvement in certain instances; however, it portends a higher risk of morbidity than conservative measures, particularly in the elderly population that is affected by a number of co-morbidities. The elderly make up the majority of patients with rotator cuff dysfunction, with marked disabilities leading to functional decline. Current conservative treatments of partial RCTs include modification of daily activity, corticosteroid injection, oral medication such as non-steroidal anti-inflammatory drugs (NSAIDs), and/or targeted physical therapy [31]. The aim of conservative management is to decrease shoulder pain and regain function while minimizing risk of further injury to the rotator cuff tendons.

A. Physical Therapy

Physical therapy (PT) mainly consists of stretching and strengthening exercises that patients perform at home following a scheduled program or under the supervision of a physical therapist [28]. The characteristics of an exercise program, however, are not standardized. An exercise program should be tailored to the location of the tear and aim to decrease stiffness and improve function and range of motion.

B. Medications

Systemic drugs for patients experiencing shoulder pain include NSAIDs. Recently, cyclo-oxygenase-2 (COX-2) selective inhibitors have also been introduced for the management of shoulder pain [28]. Both NSAIDs and COX-2 inhibitors demonstrate short-term efficacy in controlled clinical studies and both present adverse side effects. Conventional NSAIDs cause adverse gastrointestinal reactions in as many as 76% of patients [28]. NSAIDs have also exhibited adverse renal, dermatological, and neurological effects in certain instances [28]. In instances where patients have used either NSAIDs or COX-2 inhibitors for more than 3 months, concerns have arisen about potential cardiovascular risk [28, 46]. Use of such medication is therefore recommended for short periods of time. Other common adverse effects include interference with diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors (used primarily for the treatment of hypertension and congestive heart failure), and angiotensin type-2 receptor antagonists, thereby influencing control of blood pressure in patients with hypertension [28].

C. Corticosteroid injections

Several types of intra-articular injections are commonly used in clinical settings for alleviation of pain. With regards to shoulder pain treatment, Injections may be administered either into the subacromial space or to the glenohumeral and acromioclavicular joints, and they are typically administered in a solution consisting of a short-acting anesthetic, a longer-acting anesthetic, and a corticosteroid such as cortisone [55]. Corticosteroids are generally recommended in conjunction with PT and oral NSAIDs, providing more rapid relief for patients in order to undergo PT programs with less discomfort [28]. Reported outcome measures are variable, and the literature on corticosteroid injection in patients with RCTs is limited. No significant benefits were found in patients with partial RCTs with symptoms lasting longer than 6 months who had failed PT and a trial of NSAIDs [28].

An important concern is the accuracy of delivery of the medication into the desired target. A difference in the effectiveness of the intervention performed under radiographic control, commonly under ultrasound guidance for instance, has been reported in some studies [28]. Though an effective method for short-term alleviation of pain, the administration of corticosteroids into tendon structures can also limit and/or inhibit their use for periods of time. They can also cause necrosis of collagen fibers, weakness, and increased risk of rupture. For this reason, more than two injections per year, once every 6 months, is discouraged [28].

Patients enduring long-term pain may thus benefit from sodium hyaluronate injection as opposed to corticosteroids. Sodium hyaluronate is a normal component of synovial fluid and therefore works to maintain physiological joint friction because of its inherent viscosity [28]. Its efficacy has been proven in a small series of patients with RCTs, with significant benefits over placebo, and has demonstrated a lowering in pain, less need for oral analgesics, and improvement in range of motion [47]. Presenting minimal to no side effects, it seems to be a valid treatment option [47]. However, further studies are needed to confirm its efficacy.

D. Surgical intervention

Over the last two decades, surgical treatment of RCTs has shifted from the use of open repair to arthroscopic techniques including single-row and double-row anchor suture constructs as concerns over the durability and strength of initial repair methods, as well as incidence of rotator cuff re-tear, increasingly arose [12]. Open repair was the oldest surgical method used for treating RCTs, often requiring an open incision several centimeters long depending on the extent of the tear. The surgeon makes the incision over the shoulder and detaches the deltoid to better see and gain access to the torn tendon [2]. An open repair today may be a good option if the tear is large or complex or if additional reconstruction, such as a tendon transfer, is indicated [2]. Over the years, new technology and improved surgeon experience have led to less invasive surgical procedures.

Arthroscopic surgery is a minimally invasive technique that allows orthopedic surgeons to assess, and treat in certain cases, a range of conditions affecting the shoulder joint. During the procedure, the surgeon makes small incisions or portals in the affected joint and then inserts a micro camera and fiber optics to light the interior space [2, 54]. Pictures obtained with the camera are then projected onto a video screen in the operating suite (Figure 6) [2, 54]. Because the arthroscopic camera and surgical instruments are thin, the orthopedic surgeon is able to use very small cuts rather than larger incisions needed for standard, open surgery [2, 54].

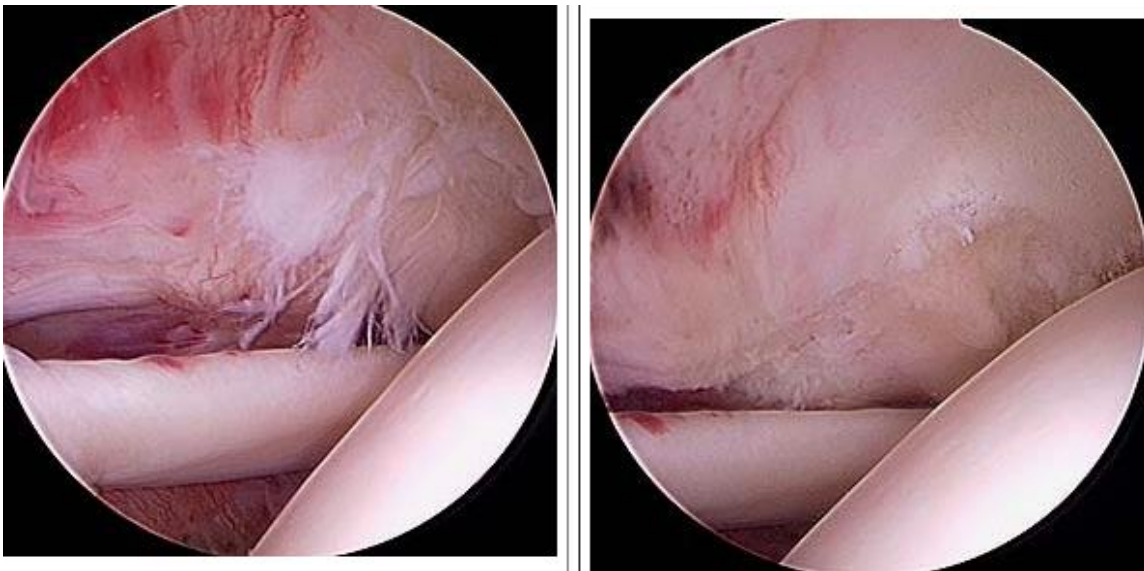


Figure 6. Arthroscopic view of a Partial Rotator Cuff Tear. The figure illustrates the image-capturing capabilities of arthroscopic camera during surgery. The left image denotes a partial rotator cuff tear at the onset of the procedure, while the right image is that of the rotator cuff after debridement of devitalized tissue.

Source: Mishra, A. Arthroscopy Pictures of a Partial Rotator Cuff Tear
Figure downloaded from <http://www.EMEDX.com>

The mini-open repair combines an open repair technique with arthroscopy to reduce the size of the incision required to perform rotator cuff repair, typically 3-5 cm in length [2]. Small portals are created to insert the arthroscopic and an additional incision is created to visualize the rotator cuff [2]. The surgeon reaches the tear by splitting the deltoid muscle along the lines of its fibers rather than detaching it fully. It is then kept in place by a temporary suture to prevent further damage while the repair is being completed. The mini-open approach thus reduces the chance of deltoid injury that may occur with a traditional open technique.

Regardless of the technique utilized, the repair of the rotator cuff itself involves suturing the torn, loose ends of the involved tendon back together and anchoring the tendon back to the humerus. A full or partial repair may be performed, depending on the severity of the tear. As its name implies, full repair is the complete repair of the tear. When a complete repair is not feasible, such as when the tear is extremely large, a partial repair may be performed in order to restore adequate function and delay the progression of the tear.

Debridement involves removing loose fragments of tendon, bursa, and other debris from the space in the shoulder where the rotator cuff moves [15]. In certain instances, the acromion may require smoothing or a portion of the bones forming the AC joint may need to be removed in order to decrease mechanical impingement of the acromion on the rotator cuff. Acromioplasty involves the removal of bone from the underside of the acromion, thus creating more room in

the subacromial space [15]. If the rotator cuff is damaged extensively, the patient may require complete rotator cuff reconstruction with a tendon obtained from elsewhere in the body [15].

RCTs are often surgically repaired when symptoms have failed to resolve with non-operative treatment [7]. Various studies have demonstrated the long-term favorable outcomes of surgical repair, with a reported 94% survivorship at 5 years and 83% at 10 years [7]. Moreover, clinical results after rotator cuff repair have shown to be satisfactory regardless of the operative technique used [24]. Average satisfaction rates of 85% have been reported for open surgery and 84%-95% for arthroscopic surgery [24].

Biological Augmentation of Rotator Cuff Tears

Despite satisfactory results, the incidence of persistent tendon defects or re-tears is still significant. 85% of surgical repair failures occur during the first six months of recovery, with 74% occurring in the first three months [7]. Two years after arthroscopic rotator cuff repair, 70% of supraspinatus repairs and only 27% of supraspinatus with infraspinatus repairs remained intact [7].

Several studies have demonstrated that native tendon-bone insertions are not fully restored after rotator cuff repair [34]. The native insertion site of the rotator cuff is composed of four zones that include the tendon itself, unmineralized fibrocartilage, mineralized fibrocartilage, and bone [36]. After being inflicted with injury, repaired tendons undergo healing through the formation of

fibrous scar tissue rather than through the regeneration of a histologically normal insertion [36]. Consequently, repaired tendons have inferior mechanical properties and are more susceptible to re-tearing. Considering the relatively high percentages of repair failure, it is thus important to explore techniques of biological augmentation to reduce the post-surgical recurrence rate and improve long-term shoulder function after rotator cuff repair [36]. Furthermore, as the degenerative torn ends of rotator cuffs do not appear to contribute to healing, coupled with the fact that tendon healing is naturally slow, an additional biological strategy is required to improve the tissue quality of torn ends and to aid the regeneration of native tendon-to-bone insertions [23].

1. Delivery of Cells and Growth Factors to the Healing Rotator Cuff

Several strategies have been proposed to enhance tendon healing, a complex process characterized by a series of events triggered by injury to the tissue itself. This sequence includes inflammation, repair, and remodeling [37]. Recently, research has focused on regenerative therapies such as the delivery of growth factors to the site of injury. Growth factors are a subset of cytokines, or soluble proteins affecting cellular behavior, that help induce cellular division, maturation, and differentiation [37].

A number of GFs are released in the repair phase of the healing process, acting through specific cell surface receptors on appropriate target cells in to promote cellular proliferation and matrix deposition. The temporal expression of various GFs varies, with some triggered as early as one week after injury. These

GFs include basic fibroblast growth factor (bFGF), bone morphogenetic protein 12, 13, and 14 (BMP-12, 13, 14), cartilage oligomatrix protein (COMP), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF- β), transforming growth factor-beta (TGF- β), and insulin-like growth factor-1 (IGF-1) [37]. GF selection, timing of application during the repair process, and method of delivery are all factors focused on in this area of rotator cuff repair research today [37].

2. Extracellular Matrix Augmentation

Scaffolds are often used in orthopedics to promote native tissue ingrowth and can be composed of either natural or synthetic materials [37]. They provide mechanical support and have biological properties that may favorably influence cellular proliferation and differentiation and consequently improve tendon-to-bone healing [8]. Additionally, scaffolds help mediate cellular recruitment and adherence, nutrient diffusion, and GF delivery [37]. Sources of scaffolds may include transplanted host tissue, naturally derived polymers such as collagen, synthetic polymers, or in situ host tissue such as biceps tendon or deltoid muscle, both of which previously been utilized to bridge a residual defect during massive cuff RCT repair [8].

3. Platelet Rich Plasma

The use of PRP injections as a promising alternative for conservative management of both degenerative and acutely injured tissues has quickly gained recognition and popularity among the scientific community. The idea of utilizing

PRP as a viable treatment option dates back to the 1990's when the first seminal paper was published on the use of PRP in augmenting maxillofacial surgery [36]. Today, clinical applications of PRP include periodontal and maxillofacial surgery, plastic surgery, treatment of chronic skin and soft tissue ulcers, treatment of bone fractures, bone tendon healing, and tendinopathies [36]. As previously mentioned, injured tendons are marked by a degenerative process and poor healing response. The most common form of tendon healing is by inflammation, but tendons taken from chronically degenerative conditions demonstrate no inflammation and poor vascularization, a factor that may account for their markedly slow healing rate. It has thus been hypothesized that improving angiogenesis and augmenting tissue remodeling by inducing the release of fundamental GFs such as vascular endothelial growth factor (VEGF) via PRP administration can positively affect healing response [19].

The theory supporting the use of PRP in treating various musculoskeletal conditions is based on the concept of reparative formation. In this context, platelets play an essential role in the healing process through the normal secretion of GFs and recruitment of reparative cells [19]. PRP is a platelet concentrate produced from a person's own blood that typically contains more than one billion platelets/ μL , a figure representing a 3- to 5-fold increase in the concentration of platelets when compared with the normal concentration present in whole blood [7, 23]. Within platelets are dense alpha granules that contain a myriad of cytokines and growth factors that help to promote wound healing.

PDGF, TGF- β , IGF-1, VEGF, bFGF, epidermal growth factor (EGF), and hepatocyte growth factor (HGF) are a few of the GFs contained within the alpha granules, which are proven to be powerful agents in stimulating duplication, activation, and growth of mesenchymal cells—mainly, osteoblasts, fibroblasts, and endothelial cells—as well as tissue regeneration [7, 23]. Furthermore, these GFs also promote cell proliferation, migration, and synthesis of ECM proteins. With such a high concentration of platelets and concurrently increased GFs, PRP thus has the potential to improve healing of rotator cuff tears.

PRP injections are widely accepted by patients because the injection is considered an autologous blood product that promotes the body's own natural healing process [19, 36]. It is prepared by drawing blood from the patient and subsequently spinning the sample in a centrifuge, a tool utilized to separate the various components of the blood (Figure 7). The platelet-concentrated component is then extracted and treated before it is administered to an injured area of bone or soft tissue such as a tendon or ligament.



Figure 7. Platelet Rich Plasma Preparation Device. One of several PRP preparation systems (GPS III Biomet, Warsaw, IN) currently available for outpatient use. PRP is commonly prepared via centrifugation, separating whole blood into its components: whole red blood cells (bottom of well), platelets, and white blood cells. Plasma can be further divided into platelet-poor plasma (top yellow column) and platelet-rich plasma (white middle column).

Source: Mishra A, Randelli P, Barr C, Talamonti T, Ragone V, Cabitza P. Platelet-rich plasma and the upper extremity. *Hand Clin.* 2012; 28(4): 481-491.

The risk of acquiring a transmitted blood-borne infection or experiencing an anaphylactic reaction is virtually nonexistent with PRP injections [31]. PRP also generally has a lower cost and shorter recovery time compared to surgical management. The use of PRP for musculoskeletal injuries has thus increased significantly over the last few years, given its safety and availability for outpatient preparation and delivery.

When evaluating the efficacy of PRP injections, it is important to consider the various PRP formulations that may be prepared and consequent differences in their biological characteristics such as GF concentration and catabolic enzyme content [36]. PRP may be prepared as a pure platelet concentrate via centrifugation (leukocyte-poor) or as a mixture with white blood cells (leukocyte-rich). [2, 36]. Additionally, white blood cells come in several varieties, comprising of neutrophils, lymphocytes, and monocytes [36]. PRP application techniques are also variable. Platelets can be activated ex vivo with thrombin and/or calcium immediately before injection [19]. A network of fibrin then forms, resulting in a membrane-like material that can be incorporated into a suture construct [2].



Figure 8. PRP Gel-Like Construct. PRP formulations often activated with calcium chloride or thrombins are prepared as a gel-like substance that are then sutured into a rotator cuff repair.

Source: Barber et al. Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. *Arthroscopy*. 2011; 27(8): 1029-1035.

This technique can result in immediate release of GFs. Use of PRP in an unactivated manner, without thrombin or calcium, allows for application via a

syringe or catheter and allow for slow activation via exposure to endogenous collagen [19, 36]. This methodology has been shown to result in up to 80% more GF release over the same period of time [36]. In surgical applications of PRP after arthroscopic repair, the formulation is often treated with calcium chloride or thrombin before being administered, allowing for formation of a gel-like clot that can be directly applied or sutured at the surgical site (Figure 8) [19, 36].

Table 1. PRP Classification. To better understand and communicate the value of PRP for sports medicine applications, Mishra et al. devised a classification system (Table 1), that categorizes various formulations of PRP based on the absence or presence of white blood cells and whether the PRP is used in an activated or unactivated form. A sub-classification is also incorporated based on the platelet concentration. Current literature on the use of PRP on rotator cuffs has studied a variety of PRP formulations, an important factor to keep in mind when trying to determine the efficacy of the treatment option for RCTs.

Source: Mishra, A., Harmon K., Woodall J., et al. Sports medicine applications of platelet rich plasma. *Curr Pharm Biotechnol* 2012; 13 (7): 1185-95.

Formulation	White Blood Cells (WBCs)	Activated?
Type 1	Increased over baseline	No
Type 2	Increased over baseline	Yes
Type 3	Minimal or no WBCs	No
Type 4	Minimal or no WBCs	Yes
---	A: >5x Platelets B: <5x Platelets	---

PUBLISHED STUDIES

Preliminary in vitro studies present compelling evidence that PRP may stimulate rotator cuff fibroblasts and increase cell proliferation related to the growth and repair of rotator cuff tissue. A study conducted by Jo et al. sought to examine the effects of PRP on tenocytes isolated and cultured from human rotator cuff tendons with degenerative tears [24]. The hypothesis put forth by the authors stated that use of a PRP gel formulation would promote tenocyte proliferation and induce matrix gene expression and synthesis.

After obtaining informed consent, tenocytes were isolated and cultured from tendon tissues of 9 patients undergoing arthroscopic rotator cuff repair for the treatment of degenerative RCT [24]. Inclusion criteria required that all patients experienced shoulder pain with an insidious onset and no history of trauma [24]. Tendon tissue pieces were 3 x 3 mm in size and obtained after debriding severely frayed portions of the lateral edge with a basket forceps [24]. To evaluate cell proliferation, tenocytes were cultured with 10% vol/vol platelet-poor plasma (PPP), PRP activated with calcium, and PRP activated with both calcium and thrombin at platelet concentrations of 100, 200, 400, 800, 1000, 2000, 4000, 8000, and 16,000 x 10³/μl for 14 days [24]. Cell number was measured at Day 7 and 14 [24]. Throughout the experiments, cells treated with 2% fetal bovine serum (FBS) were used as controls [24].

To investigate matrix gene expression and synthesis, cells were cultured with a PPP or PRP gel (10% vol/vol) at a platelet concentration of $1000 \times 10^3/\mu\text{l}$ for 14 days [24]. Quantitative real-time reverse transcriptase polymerase chain reaction (PCR) was then performed to determine the expressions of type I and III collagen, decorin (a proteoglycan that binds to type I collagen fibrils and plays a role in matrix synthesis), tenascin-C (a glycoprotein expressed in the ECM), and scleraxis. Measurements of total collagen and glycosaminoglycan (GAG) synthesis were conducted at Days 7 and 14 [24].

The authors found that PRP activated with calcium or a combination of calcium and thrombin significantly increased cell proliferation at days 7 and 14 in a dose-dependent manner, while the addition of thrombin alone moved forward the plateau of cell proliferation (Figure 9). At Day 7, PRP activated with calcium at a platelet concentration of 4000×10^3 cells/ μL demonstrated the greatest cell proliferation, with an approximately 5-fold increase, compared with the control [24]. At Day 14, the highest proliferation was observed at 8000×10^3 cells/ μL for PRP-Ca and at $16,000 \times 10^3$ cells/ μL for PRP-Ca-Thrombin [24]. PRP also significantly induced the gene expression of type I collagen at day 7 but not at day 14, and it significantly promoted the genetic expression of type III collagen both at days 7 and 14 [24]. The ratio of type III/I collagen did not change by a statistically significant value at days 7 and 14 [24]. The expressions of decorin and scleraxis significantly increased at day 14, whereas that of tenascin-C

significantly increased at days 7 and 14 [24]. Finally, PRP significantly increased total collagen synthesis at days 7 and 14 and GAG synthesis at day 14 [24].

The results of the study demonstrated that PRP significantly promoted cell proliferation of tenocytes from human rotator cuff tendons with degenerative tears as well as enhance matrix gene expression. Total collagen production and GAG synthesis was significantly increased as well with PRP [24]. PPP, however, was ineffective in stimulating the proliferation of tenocytes or inducing the expression and synthesis of tendon matrix aside from decorin at day 14 and total collagen. Such findings allude to the importance of bioactive materials released from granules in the platelet. The addition of thrombin for activation significantly accelerated cell proliferation, particularly at lower concentrations, compared to the addition of calcium. This result is most likely due to the initial burst release of growth factors upon the addition of thrombin. Taken together, the results of the study suggest that PRP might be used as a useful biological tool for regenerative healing of RCTs by enhancing the proliferation and matrix synthesis of tenocytes from tendons with degenerative tears.

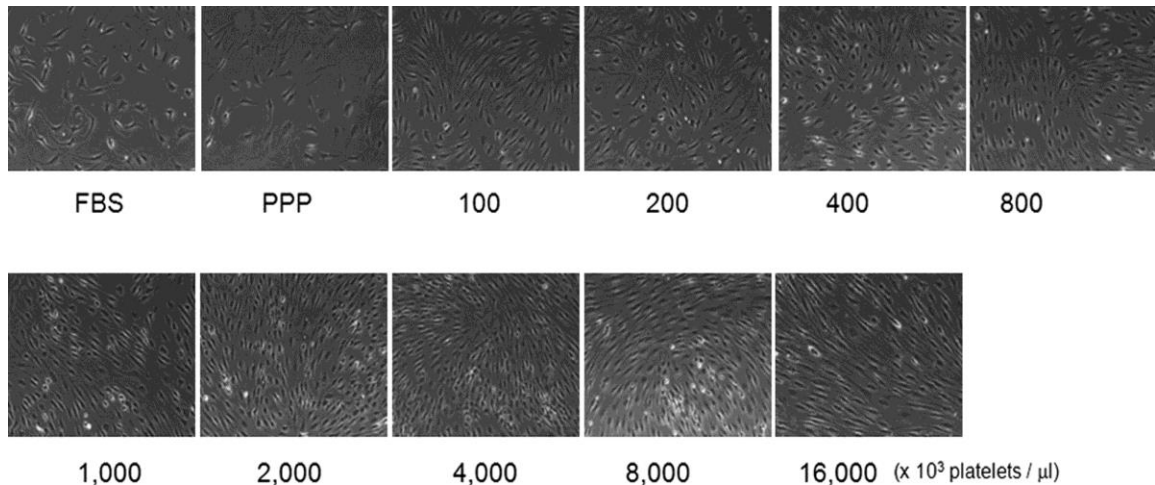


Figure 9. Tenocytes isolated and cultured from human rotator cuff tendons.

Tenocyte cells were isolated from tendon tissue samples and cultured for 14 days with a PRP gel (10% vol/vol) at platelet concentrations of 100, 200, 400, 800, 1000, 2000, 4000, 8000, and 16,000 $\times 10^3$ cells/ μ L. Fetal bovine serum (FBS) and platelet-poor plasma (PPP) wells were used as controls for comparison. Note that cell proliferation increases with increasing platelet concentration before reaching a maximum concentration at 4000 $\times 10^3$ cells/ μ L and leveling off afterwards.

Source: Jo CH, Kim JE, Yoon KS, Shin S. Platelet-rich plasma stimulates cell proliferation and enhances matrix gene expression and synthesis in tenocytes from human rotator cuff tendons with degenerative tears. *Am J Sports Med.* 2012; 40(5): 1035-1045.

A study conducted by Hoppe et al. also sought to examine the effect of PRP on cell proliferation and gene expression and synthesis of collagens and ECM proteoglycans by studying tenocytes that were isolated from chronically retracted rotator cuff tendons and stimulated afterwards with locally applied platelet-released growth factors (PRGF) [22]. Tenocytes from eight patients with chronic RCTs were cultured for four weeks in 2 different media: standard medium and media with an additional 10% PRGF [22]. Cell proliferation was then assessed at days 7, 14, 21, and 28 [22]. Messenger RNA (mRNA) levels of

collagen I, II, and X, decorin, biglycan, and aggrecan—all components of connective tissue that play a role in ECM assembly--were analyzed using real time reverse transcriptase PCR [22]. It was found that the proliferation rates of tenocytes were significantly higher at all time points when cultured with PRGF. After remaining in culture for 21 days, the mRNA levels for collagen I, II, X, decorin, aggrecan, and biglycan were all significantly higher in the PRGF medium [22]. Locally applied GFs therefore seem to enhance tenocyte proliferation in vitro and promote synthesis of ECM components to levels similar to those found with insertion of the normal human rotator cuffs. The positive results obtained in this study provide compelling evidence for the biological augmentation of repaired rotator cuffs with other sources of GFs such as PRP.

A limitation of the two previous studies pointed out by Sadoghi et al. is that they attempt to assess the clinical impact of PRP on the rotator cuff without first attempting to establish a dose-response model or track a longer period of time after PRP stimulation [45]. Evidence from in vitro and animal studies suggest that the pro-inflammatory agents of PRP might have negative effects, and its use and dosage should be chosen deliberately while carefully weighing the benefits with potential detrimental effects such as muscle fibrosis after injury [45]. The authors therefore sought to elucidate the effects of PRP on rotator cuff fibroblast growth and bioactivity, with special attention on the dose-response relationship between various PRP concentrations and these outcomes in order to arrive at an optimal

dose of PRP concentration to maximize cellular stimulation while reducing potential risk [45].

Rotator cuff fibroblasts of six patients undergoing arthroscopic cuff tear reconstruction were cultured in vitro for 21 days and stimulated with PRP in three different concentrations: 1-fold, 5-fold, and 10-fold [45]. Samples were obtained for DNA and GAG measurement at 1, 7, 14, and 21 days [45]. The biological outcomes were then regressed on the PRP concentration. The authors found that the stimulation of fibroblasts with PRP significantly influenced the level of cellular proliferation and activity of the human rotator cuff with elevated GAG and DNA levels. The dosage of PRP had the significantly highest impact on this proliferation using a 1-fold or 5-fold application [45]. PRP therefore was found to have a significant effect on fibroblast proliferation of the human rotator cuff in vitro, with an optimal benefit using a one- to five-fold PRP concentration [45].

Follow-up animal studies also demonstrate that PRP may help accelerate healing, increase vascularization, and heighten fibroblast response when delivered to tendons at the time of arthroscopic rotator cuff repair. A study conducted by Hapa et al. sought to determine the effects of local autologous PRP injection on tendon-to-bone healing using a previously described rotator cuff repair model in rats [20]. 83 total adult male rats were involved in the experiment, 68 of which were directly included in the study and underwent left shoulder rotator cuff repair surgery [20]. The 15 remaining rats were used to collect blood for PRP production [20].

The 68 rats were next divided into two even groups: the PRP group and a control group. The left shoulders of the rats were operated on and the deltoid muscle and acromioclavicular arch were retracted in order to achieve complete exposure of the rotator cuff tendon [20]. The supraspinatus tendon was then detached from the anterior part and the remaining fibrocartilaginous tissue was removed [20]. A 2 mm deep hole was drilled into the ensuing bleeding bone and 150 μ L of PRP was applied to the hole [20]. An additional 150 μ L of PRP was injected to the repair site intraoperatively [20]. In the control group, saline injections of the same amount were applied intraoperatively instead [20].

The treated rats were next divided into four equal groups of 17: PRP group (week 2), control group (week 2), PRP group (week 4), and control group (week 4) [20]. After 2 weeks and 4 weeks, rats in both the PRP group and control group of each respective week were euthanized (34 total rats at a time) [20]. Histological analysis using a semi-quantitative scoring system was performed on 7 rats per group [20]. Tendon integrity, increases in vascularity and inflammatory cells, and the degree of new bone formation were evaluated and compared between the groups [20]. Biomechanical analysis of the remaining tendons, 10 rats per group, was performed as well.

Results showed that the degree of inflammation and angiogenesis were lower in the PRP study groups than the control groups, both at weeks 2 and 4, by a statistically significant amount [20]. New bone formation was detected in the control group after 4 weeks as well [20]. Biomechanically, tendon thickness and

continuity were stronger in PRP-treated specimens 2 weeks postoperatively [20]. This may be due to the early effects of platelets on tendon healing. The authors reference a study conducted by Kajikawa et al., which reported an increase in circulation-derived cells infiltration to the wounded area and proliferation of cells with enhanced collagen synthesis at one or two weeks after injury [26]. The cell levels subsequently returned to normal [26]. Another reason could be that the rotator cuff heals expeditiously in a rodent model, making the difference virtually undetectable 4 weeks after injury.

Hapa et al. thus concluded that local autologous PRP injections might have beneficial effects on initial rotator cuff tendon-to-bone healing and enhance initial tendon-to-bone healing remodeling [20]. This represented a relevant clinically finding, as no prior prospective randomized controlled clinical studies or experimental in vivo studies had been conducted to demonstrate the effect of PRP on rotator cuff tendon healing.

Most studies investigating the efficacy of PRP in rotator cuff repair have focused on the use of PRP scaffolds during arthroscopic surgical repair. A comprehensive review of five studies investigating PRP in arthroscopic rotator cuff repair (Table 2) found no significant difference in the re-tear rates or pain improvements between patients who did and did not receive PRP at the time of surgery [11]. The authors of this review are quick to admit, however, that the clinical heterogeneity among their study selections is a valid concern. The repair techniques of three of the studies examined, for instance, was single-row as

opposed to the double-row repair techniques used by the other two. Additionally, there were noted differences in rotator cuff tear sizes and the number of tendons involved among the five studies. Furthermore, three different PRP formulations were used among the studies included. Differences among the various PRP products included the volume of autologous blood that was drawn, rates at which the blood was centrifuged, spin cycles utilized, the use of an activator, and white blood cell concentrations, as well as final platelet and GF concentrations [11].

Table 2. Baseline Characteristics of Studies Examined in Systematic Review of the Role of PRP in Arthroscopic Rotator Cuff Repair. The repair techniques of 3 of the studies was single-row as opposed to double-row. Additionally, there were noted differences in rotator cuff tear sizes and the number of tendons involved among the five studies. 3 different PRP formulations were used among the studies as well.

Study	Study Design	Inclusion Criteria	Details of Surgery	PRP Formulation	Sample Size (% Male)	Mean Age (yr)	Follow-up Rate (%)	Mean Follow-up (mo)	Outcome Measures	Definition of Rotator Cuff Retear
Castricini et al. ²⁸ (2011)	Level I randomized	Isolated repairable supraspinatus tear	DR 1 Medial double-loaded anchor + 2 lateral-row anchors	Cascade PRP fibrin matrix construct (Musculoskeletal Transplant Foundation)	88 (45.5)	55.3	Clinical, 100 MRI, 88.6	20.2	Constant score (primary outcome) Retear rate—MRI	Full-thickness tear defined as absence of visible tendon fiber extending across entire tendon from inferior to superior
Randelli et al. ²⁹ (2011)	Level I randomized	FTRCT confirmed intraoperatively (all sizes)	SR Mean no. of SA, 2 (PRP) or 1.6 (no PRP)	GPS II (Plasmax Platelet Concentration System; Biomet Biologics)	53 (39.6)	60.5	Clinical and MRI/US, 85	Clinical, 24 MRI/US, 21 with PRP and 23 with no PRP	Constant score (primary outcome) SST score UCLA score VAS score for pain Retear rate—MRI and US	Lack of continuity of tendon in 1 slice of coronal plane; very thin bands of tissue were identified as failure of healing
Barber et al. ³⁰ (2011)	Level III case-control study	1- or 2-tendon FTRCT measuring 10-50 mm in width; stage 2 FI or lower	SR 1 or 2 double-loaded SA	Cascade PRP fibrin matrix construct (Musculoskeletal Transplant Foundation)	40 (67.5)	57	100	Clinical, 31 MRI, 4	ASES score Constant score Rowe score SANE score SST score Retear rate—MRI (primary outcome)	Full-thickness rotator cuff defect
Bergeson et al. ³² (2012)	Level III prospective cohort with historical control	High-risk tears included per algorithm score $\geq 3^*$; minimum age, 50 yr; minimum tear size, 2 cm	SR in majority Mean no. of SA, 2.9 in PRP/no PRP groups	Cascade PRP fibrin matrix construct (Musculoskeletal Transplant Foundation)	38 (NR)	65.0	Clinical and MRI, 97.3	Clinical, 12 for PRFM and 27 for no PRFM MRI, 12	ASES score Constant score SANE score UCLA score WORC score Retear rate—MRI	Full-thickness defect in repaired tendon in which no fibers were visualized spanning defect in any MRI plane
Jo et al. ³¹ (2011)	Level II prospective cohort with concurrent control	FTRCT (all sizes)	DR suture bridge technique 2-5 medial-row SA + lateral-row anchors	Plateletpheresis system with leukoreduction set (COBE Spectra LRS Turbo; Caridian BCT)	42 (45.2)	60.7	Clinical, 100 MRI, 76.2	18.9 for PRP 20.3 for no PRP	ASES score Constant score DASH score SPADI SST score UCLA score Retear rate—MRI	Sugaya method ³³ ; type IV/V—presence of minor or major discontinuity in repaired tendon

In a randomized study conducted by Barber et al., 40 patients underwent arthroscopic repair of a torn rotator cuff [5]. Two matched groups, 20 patients each, were included: patients undergoing rotator cuff repairs without PRP fibrin matrix augmentation and patients undergoing repair augmented with two sutured PRP constructs [5]. A single-row rotator cuff repair to the normal footprint, without tension or marrow vents, was performed by a single surgeon [5]. Postoperative rehabilitation was held constant for all patients participating in the study. An abduction sling was used to immobilize patients for the first 3 weeks postoperatively and converted to a traditional sling for an additional 3 weeks to take the arm out of abduction and provide more mobility [5]. At 6 weeks, a home exercise program was initiated as well as passive range of motion exercises under the guidance of a physical therapist [5]. Postoperative MRI scans were obtained at 4 months after progressive strengthening above the shoulder had begun and used to evaluate rotator cuff healing [5].

The authors' findings showed that twenty patients who received PRP were shown to have improved rates of tendon healing and lower rates of re-tearing on MRI as compared to controls [5]. Postoperative MRI studies showed a 60% re-tear rate (12 of 20) in the control group compared to a 30% re-tear rate (6 of 20) in the PRP group [5]. Of the 14 tears in the control group initially less than 3 cm in anteroposterior length, 7 healed for a 50% rate of healing. Of the 14 tears in the PRP construct group that were initially less than 3 cm in length, however, 12 healed for an 86% heal rate [5]. Interestingly though, the two patient groups did

not self-report significantly different improvements in pain and function or display significantly disparate clinical outcomes.

A similar study by Jo et al, demonstrated compelling evidence of increased healing rate and decreased re-tear incidence among post-arthroscopic repair with PRP patients as visualized on MRI [23]. In this prospective cohort study, 42 patients with full-thickness rotator cuff tears were included. Patients were informed about the use of PRP before surgery and decided for themselves whether to have PRP administered at the time of surgery [23]. 19 patients underwent arthroscopic rotator cuff repair with PRP and 23 without [23]. PRP was prepared via plateletpheresis and applied in the form of a gel threaded to a suture and interposed between tendon and bone. Outcomes were assessed preoperatively and then again 3, 6, 12, and 16 months after surgery [23]. Clinical outcomes included pain, range of motion, strength, and overall satisfaction. Pain was evaluated using the visual analog scale (VAS) and accounted for pain at rest, in motion, and at night [23].

Average pain scores were also measured and compared. Strength measured the strength of the supraspinatus, infraspinatus, and subscapularis muscles specifically and was determined using a number of functional scoring systems: the American Shoulder and Elbow Surgeons (ASES) system, the University of California at Los Angeles (UCLA) system, the Disabilities of the Arm, Shoulder, and Hand (DASH) system, the Simple Shoulder Test (SST), and the Shoulder Pain and Disability Index (SPADI) system [23]. Overall satisfaction

was evaluated using a series of yes/no questions concerning the patient's willingness to undergo surgery again, whether they would recommend surgery to others, and whether they were able to perform daily tasks and work as they did prior to injury [23]. MRI also assessed the structural integrity of the repaired tendons at a minimum of 9 months postoperatively. Small and medium size tears were grouped as <30 mm and large and massive tears as >30 mm [23].

The authors determined that PRP gel application to arthroscopic rotator cuff repairs did not accelerate recovery with respect to pain, range of motion, strength, functional scores, or overall satisfaction as compared to conventional repair methods at any time point analyzed. Whereas MRI demonstrated a re-tear rate of 26.7% in the PRP group and 41.2% in the conventional group, there was no statistically significant difference between the two groups [23]. The results therefore suggest that PRP application during arthroscopic repair did not clearly demonstrate accelerated recovery clinically or anatomically except for an improvement in internal rotation. Nevertheless, as the study may have been underpowered to detect clinically important differences in the structural integrity, additional investigations are necessary to further determine the effect of PRP. These may include the optimization of PRP preparations and a larger randomized study powered for healing rate.

Another arthroscopic study conducted by Randelli et al. showed that patients who received PRP reported significantly improved shoulder pain and function as compared to control patients [42]. In their prospective, randomized,

controlled, double-blind study, 53 patients who underwent arthroscopic rotator cuff repair of a complete tear were divided into two groups: a treatment group consisting of patients receiving a PRP injection with autologous thrombin during repair and a control group [42]. Patients were evaluated using several validated outcome scores similarly used by Jo et al. (VAS, SST, and UCLA systems) as well as the Constant score and strength in external rotation (SER) system [42]. The Constant score was calculated following a detailed physical examination in a standardized fashion. The SER was measured in a sitting position with the arms neutralized [42]. Pain was assessed using VAS at 3, 7, 14, and 30 days after surgery [42]. Structural integrity of repaired tendons was assessed via MRI at a minimum of 12 months post-operation, with the exception of 3 patients who declined the MRI and were evaluated by ultrasound [42].

The study showed that pain scores of those in the treatment group were significantly lower than those in the control at 3, 7, 14, and 30 days after surgery [42]. SST, UCLA, Constant, and SER scores were also significantly higher in the treatment group at 3 months after surgery; however, no significant differences were noted after 6, 12, and 24 months [42]. In addition, healing rates observed on follow-up radiography was not significantly improved in the treatment group [42]. The overall findings of the study nonetheless suggest an accelerated repair of rotator cuff utilizing PRP application.

DISCUSSION

The treatment of RCTs in general has made significant advancements over the past few decades, utilizing a mixture of both conservative and non-conservative measures in an attempt to arrive at optimal healing and relief of pain. Despite conflicting and inconsistent results, a number of published studies to date illustrate a general trend towards the effectiveness of PRP treatment, suggesting that it may improve patient outcomes and prevent the need for future surgery in patients with partial RCTs. Nonetheless, it is still difficult to draw definitive conclusions on the efficacy of PRP in rotator cuff repair because of the heterogeneous nature in which PRP studies are established.

As is evident from even the few published studies examined within this literature review, clinical studies on PRP conducted thus far all have different experimental designs and strength of evidence. These trials have used various PRP formulations such as application of activated PRP or incorporation of platelet rich fibrin matrix into the repair. Debates continue to exist on the optimal concentration of platelets and GF release in PRP formulations that is necessary for muscle and tendon healing. Clinically effective PRP has been defined as having a minimum of four times the normal concentration of platelets, though efficacy has been demonstrated with less concentrated preparations [19]. Additionally, the surgical techniques and rehabilitation protocols for patients were

not standardized across the trials, making it difficult to assess patient outcome measures with regards to PRP in these cases.

Though the use of PRP injections is considered safe and acceptable among clinicians and patients, the cost of any new therapeutic modality like PRP is important to take into consideration, particularly within the current cost-conscious environment of the US healthcare system. Because of the variances in formulation and different preparation systems available for outpatient use, the cost of PRP injections is largely dependent on distributing companies and the relationship of institutions utilizing PRP injections with these outside sources [19]. Additionally, because PRP treatment is still widely regarded as an experimental or investigational treatment, many health insurance plans do not reimburse the cost of PRP or other autologous blood injection treatments. Taking into account the cost of preparation, as well as hospital and radiology fees accompanying the procedure, the average cost of a single PRP injection is nearly \$2700 (Appendix 1). It is therefore wise for patients to weigh treatment options before opting to undergoing PRP treatment.

Though not a life-threatening injury, the pain and discomfort associated with RCTs and shoulder pain can significantly decrease the value of a patient's lifestyle, hindering one from performing daily activities and accomplishing goals as adequately and frequently as one would like. The use of PRP as a minimally invasive treatment option with the prospect of a speedier recovery time and less morbidity post-treatment, as opposed to surgical interventions, is thus a highly

attractive option and one that ought to be further investigated. The use of PRP treatment also has significant implications for a number of athletes wishing to return to form from injury as quickly as possible. Currently, the World Anti-Doping Agency prohibits the administration of endogenous GFs in all elite sports that may affect muscle, tendon, or ligament protein synthesis and/or degradation, vascularization, energy utilization, and regenerative capacity [53]. Despite the presence of GFs, the use of PRP and other platelet-derived preparation were removed from the prohibited list in 2011 once studies demonstrated that they do not demonstrate any potential for performance enhancement beyond a potential therapeutic effect [56].

Currently, there are few published studies that specifically investigate the safety and efficacy of PRP injections to the shoulder as a non-operative treatment option for PT RCTs. Even fewer studies seek to compare pre- and post-injection imaging to radiographically assess healing of the partially torn tendon and, at the same time, to determine a correlation between objective (i.e. image reporting) and subjective (i.e. patient report) outcome data. As PRP continues to evolve, more substantiated research is needed to understand its mechanism of action in addition to clinical data. It is also clear that large, multicenter clinical trials are needed to define the best type of PRP to be used and for what specific clinical application. The data supporting PRP use thus far are immature, but this biologic technology has the potential to transform the practice of musculoskeletal medicine and orthopedic surgery.

APPENDIX

HOSPITAL
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SPECIAL
SURGERY



DEPARTMENT
OF
RADIOLOGY
AND
IMAGING

Dear Patient:

You have been scheduled for a Platelet Rich Plasma (PRP) injection or Autologous Blood Injection under ultrasound guidance to be performed in the Department of Radiology and Imaging at Hospital for Special Surgery.

Most health insurance plans consider this treatment experimental or investigational and therefore do not cover PRP therapy and PRP (autologous blood) related therapies. Because the health insurance plans below have notified us that these therapies are not covered, we can not bill these health insurance plans for this service.

- **The attached Advance Notice of Non-Coverage form must be signed by all patients undergoing these procedures and full payment must be made prior to treatment.** If your health insurance plan is not listed below you may select any Option. If your health plan is listed below you may select only Option 2 or Option 3.

Health insurance plans with confirmed non-coverage policies on PRP and PRP related therapies:

- AETNA
- BLUE CROSS BLUE SHIELD
- CIGNA HEALTH PLANS
- HEALTH NET
- OXFORD HEALTH PLANS
- UNITED HEALTHCARE

Please read the *Notice* as well as the attached *Patient Instructions* thoroughly so you understand your Options. Questions regarding these procedures can be directed to the Radiology Nurse at (212) 774-7111.

If you do not wish to continue with this procedure, please inform our scheduling office at (212) 774-2052 and please discuss alternate treatment options with your physician overseeing your care.

Thank you for choosing the Department of Radiology and Imaging at the Hospital for Special Surgery for your musculoskeletal care and the physicians of the HSS *Radiologists*.

Thank you

535 East 70th Street, New York, NY 10021 • Tel (212) 606-1015 • Fax (212) 774-2725 • web site: www.hss.edu or email: radinfo@hss.edu

Patient Name: _____ (Patient ID# _____)

ADVANCE NOTICE OF NONCOVERAGE

INJECTION OF AUTOLOGOUS PLATELET-RICH PLASMA (PRP) UNDER IMAGE GUIDANCE

NOTE: If your Health Benefits Plan does not pay for this treatment, you may have to pay.

Your Health Benefits Plan does not pay for everything, even some care that you or your health care provider have good reason to think you need.

We expect that your Health Benefits Plan may not pay for the injection of autologous platelet-rich plasma (PRP) under image guidance. The reason your Health Benefits Plan may not pay is because the treatment may be considered experimental, investigational or unproven for any indications or conditions.

The estimated cost of this treatment is \$2,636.10. This includes Hospital and Radiologists fees.

WHAT YOU NEED TO DO NOW:

- Read this notice, so you can make an informed decision about your care.
- **Ask us any questions that you may have after you finish reading.**
- **Choose an option below about whether to receive this treatment**

OPTIONS:	Check only one box. We cannot choose a box for you.
<input type="checkbox"/>	OPTION 1. I want the treatment listed above. I agree to pay now, but I also want my Health Benefits Plan asked for a formal decision on service coverage and payment unless it has already advised HSS within the past 30 days that it does not cover or pay for the service. I understand that if my Health Benefits Plan doesn't agree to cover or pay for the service, I am responsible for payment, but I may be able to appeal this decision by my Health Benefits Plan by following my Health Benefits Plan's instructions. If my Health Benefit Plan does pay, you will refund any payments I made to you, less co-pays or deductibles.
<input type="checkbox"/>	OPTION 2. I want the treatment listed above, but do not bill my Health Benefits Plan. I agree to pay now. I understand that I cannot appeal because my Health Benefits Plan will not be billed.
<input type="checkbox"/>	OPTION 3. I don't want the treatment listed above.

This notice gives our opinion, not an official decision by your Health Benefits Plan.

Signing below means that you have received and understand this notice, and that you agree to be personally and fully responsible to HSS for all fees for this treatment:

Signature of Patient/ _____
Parent/Guardian/Healthcare Agent
Relationship to Patient _____ Date: _____

Witness Certification: I certify that I have witnessed the person whose signature appears above signing this Advance Notice of Noncoverage.

signature of Witness _____ Date _____

Patient Name: _____ (Patient ID# _____)

ADVANCE NOTICE OF NONCOVERAGE

INJECTION OF AUTOLOGOUS BLOOD UNDER IMAGE GUIDANCE

NOTE: If your Health Benefits Plan does not pay for this treatment, you may have to pay.

Your Health Benefits Plan does not pay for everything, even some care that you or your health care provider have good reason to think you need.

We expect that your Health Benefits Plan may not pay for the injection of autologous blood under image guidance. The reason your Health Benefits Plan may not pay is because the treatment may be considered experimental, investigational or unproven for any indications or conditions.

The estimated cost of this treatment is \$2393.82. This includes Hospital and Radiologists fees.

WHAT YOU NEED TO DO NOW:

- Read this notice, so you can make an informed decision about your care.
- **Ask us any questions that you may have after you finish reading.**
- **Choose an option below about whether to receive this treatment**

OPTIONS: Check only one box. We cannot choose a box for you.
<input type="checkbox"/> OPTION 1. I want the treatment listed above. I agree to pay now, but I also want my Health Benefits Plan asked for a formal decision on service coverage and payment unless it has already advised HSS within the past 30 days that it does not cover or pay for the service. I understand that if my Health Benefits Plan doesn't agree to cover or pay for the service, I am responsible for payment, but I may be able to appeal this decision by my Health Benefits Plan by following my Health Benefits Plan's instructions. If my Health Benefit Plan does pay, you will refund any payments I made to you, less co-pays or deductibles.
<input type="checkbox"/> OPTION 2. I want the treatment listed above, but do not bill my Health Benefits Plan. I agree to pay now. I understand that I cannot appeal because my Health Benefits Plan will not be billed.
<input type="checkbox"/> OPTION 3. I don't want the treatment listed above.

This notice gives our opinion, not an official decision by your Health Benefits Plan.

Signing below means that you have received and understand this notice, and that you agree to be personally and fully responsible to HSS for all fees for this treatment:

Signature of Patient/ _____
Parent/Guardian/Healthcare Agent
Relationship to Patient _____ Date: _____

Witness Certification: I certify that I have witnessed the person whose signature appears above signing this Advance Notice of Noncoverage.

signature of Witness Date

Your physician has sent you for an image-guided injection. It is either for PRP or Autologous Blood injection. The following are answers to frequently asked questions.

LIST OF JOURNAL ABBREVIATIONS

Acta Biomed	Acta Biomedica
Acta Orthop Traumatol Turc	Acta Orthopaedica et Traumatologica Turcica
Am J Orthop	The American Journal of Orthopedics
Am J Phys Med Rehabil	American Journal of Physical Medicine & Rehabilitation
Am J Physiol Regul Integr Comp Physiol	American Journal of Physiology-Regulatory, Integrative & Comparative Physiology
Am J Sports Med	The American Journal of Sports Medicine
Arthritis Care Res	Arthritis Care & Research
Br J Sports Med	British Journal of Sports Medicine
Clin Orthop Relat Res	Clinical Orthopaedics and Related Research
Curr Rev Musculoskelet Med	Current Reviews in Musculoskeletal Medicine
Hand Clin	Hand Clinics
J Am Acad Orthop Surg	Journal of the American Academy of Orthopaedic Surgeons
JBJS	The Journal of Bone & Joint Surgery
J Bone Joint Surg Br	The Bone & Joint Journal
J Cell Physiol	Journal of Cellular Physiology
J Shoulder Elbow Surg	Journal of Shoulder and Elbow Surgery
Med Sport Sci	Medicine and Sport Science

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CURRICULUM VITAE

