



ELSEVIER

Biologic Augmentation of Rotator Cuff Repair: The Role of Platelet-Rich Plasma and Bone Marrow Aspirate Concentrate

Anirudh K. Gowd, BS,^{*} Brandon C. Cabarcas, BS,^{*} Rachel M. Frank, MD,[†] and Brian J. Cole, MD, MBA^{*}

Rotator cuff tears are common and can be a debilitating problem for patients, leading to pain, difficulty sleeping, and poor function. Although in many cases, patients can be managed non-operatively, surgery is required for a subset of patients. Even with advances in surgical techniques and implants, postoperative re-tear rates range from 15%-40%. Thus, surgical approaches to manage rotator cuff tears must be optimized to improve clinical outcomes and reduce failure rates. The incorporation of biologic agents to the repair construct has been increasingly described over the past decade, and appears to be a promising potential augmentation to standard repair techniques. Biologic agents such as platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMAC) are obtained from the patient at the time of rotator cuff repair (RCR), and are added to the repair construct to improve the likelihood of tendon healing. This review will describe the utilization of biologic agents, including PRP and BMAC, during RCR, with an emphasis on techniques and outcomes. Given the paucity of literature describing long-term outcomes with any biologic agent as an augmentation to RCR, additional research is needed to better understand the long-term impact of these agents. Oper Tech Sports Med ■■■■-■■■ © 2017 Elsevier Inc. All rights reserved.

KEYWORDS rotator cuff repair, platelet-rich plasma, bone marrow aspirate concentrate, surgical outcomes

Introduction

It is estimated that the lifetime incidence of sustaining a rotator cuff tear (RCT) is between 25% and 40%, and is significantly greater in patients over 80 years of age.¹ Given the aging population of the United States, rotator cuff pathology, including RCTs, is likely to continue to place increasing demand on the overall healthcare system. RCTs are responsible for approximately 4.5 million physician visits each year.² With advances in arthroscopic techniques, surgical instrumentation, and implants over the past decade, rotator cuff repair (RCR) for

patients diagnosed with RCT has increased from 36.8% in 2005 to 46.0% in 2012.^{3,4} Rotator cuff repair (RCR) has been shown to result in statistically significant increase in patient-reported outcomes (PROs), including the University of California at Los Angeles (UCLA) rating scale and the American Shoulder and Elbow Surgeons (ASES) shoulder index, following both single row and double-row repairs.⁵⁻⁷ Unfortunately, the rate of tendon re-tear is concerning, with rates estimated to be as high as 15%-40%, independent of the surgical technique used.^{8,9} Asymptomatic re-tears, following initial repair may also be present, which can slowly progress to larger, symptomatic tears that may lead to additional surgery.⁵ For these reasons, research efforts toward improving outcomes following RCR have increased, resulting in a variety of improvements in indications and surgical decision-making, novel surgical techniques, and advances in rehabilitation protocols. In addition, the incorporation of biologic agents to the RCR construct has been increasingly described over the past decade and appears

^{*}Department of Orthopedic Surgery, Division of Sports Medicine, Rush University Medical Center, Chicago, IL.

[†]Department of Orthopedics, CU Sports Medicine, University of Colorado School of Medicine, Aurora, CO.

Address reprint requests to Brian J. Cole, MD, Department of Orthopedic Surgery, Division of Sports Medicine, Rush University Medical Center, Chicago, IL. E-mail: bcole@rushortho.com

to be a promising potential augmentation to standard repair techniques. Biologic agents such as platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMAC) are obtained from the patient at the time rotator cuff repair (RCR), and are added to the repair construct in an effort to improve the biologic environment of the tendon-bone interface.

Tendon-Bone Healing Overview

Following tendon injury, several physiologic processes occur to initiate the healing process. *Acute inflammation* is the initial response, involving recruitment of leukocytes, platelets, and red blood cells to the site of injury.¹⁰ Platelets provide blood clots that limit blood loss and signal molecules to remove dead tissue and begin the repair process. Activated blood clots both release and recruit a host of growth and chemotactic factors that signal progenitor cells to begin the recovery process by differentiating into osteoblasts and fibroblasts to rebuild injured tissue.¹¹ Growth factors that contribute to tendon healing include transforming growth factor- β (TGF- β), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), in addition to a series of interleukins and colony stimulating factors.¹² Leukocytes also are responsible for continuing the inflammatory process and for recruiting additional growth factors for repair. The next stage is *proliferation*, beginning approximately 2 days after the injury, at which time recruited cells stimulate the synthesis of collagen and extracellular matrix.¹¹ Tenocytes secrete type III collagen into a temporary matrix. During the *remodeling* stage, which occurs 1-2 months after injury, the type III collagen is replaced by type I collagen.¹¹ Biologic augmentation takes advantage of the body's natural healing process to facilitate RCR.

Type I collagen is the main structural collagenous component of tendon tissue (>95%), providing the molecular structural support that translates to tensile strength.¹³ Tendons are composed of relatively small amounts (<5%) of other collagen types (III, IV, and V).¹⁴ Several authors have shown that tendons that have undergone degenerative changes contain fewer amounts of type I collagen, and increasing amounts of type III collagen.^{13,15} An analysis of tendinopathic human rotator cuff tendons by Riley et al. demonstrated that 82% (14/17) of supraspinatus tendons and 100% of subscapularis tendons (8/8) from patients in their study with tendinitis contained more than 5% type III collagen. In addition, Maffulli et al. showed that cultures from ruptured or tendinopathic Achilles tendons contained increasing amounts of type III collagen.⁵

Platelet-Rich Plasma

Basic Science Background

Growth factors required for tendon healing as well as hepatic growth factor (HGF), endothelial growth factor (EGF), and connective tissue growth factor (CTGF), are contained within alpha-granules of platelets and released upon

degranulation.^{16,17} Platelet-rich plasma (PRP), which can be obtained via an autologous peripheral blood draw, utilizes these factors to facilitate physiologic healing to injured tissue. PDGF, for example, plays a critical role in bone remodeling as it can induce differentiation of osteogenic progenitor cells, but also helps in recruitment of fibroblasts that are needed for tendon remodeling.¹⁸ In addition, PDGF increases expression of VEGF to increase blood supply to the area.¹⁹ Platelets also perform a chemotactic role with respect to neutrophils, though it is controversial as to whether this is beneficial due to the introduction of additional growth factors, or harmful from introduction of inflammatory cytokines such as TNF- α , IL-6, and IFN- γ .²⁰

The therapeutic application of PRP was initially described in 1987 in the setting of cardiac surgery.²¹ Over the past 30 years, the therapeutic utility of PRP has grown, and is used in a wide variety of medical fields, including orthopedics, dental and maxillofacial surgery, and veterinary medicine. Notably, the basic science of growth factors released via the degranulation of platelets have been well-studied in the rotator cuff literature. Hee et al.²² demonstrated the efficacy of using recombinant PDGF-BB during RCR in an ovine model by demonstrating an increased load to failure tolerated by tendon repaired with increasing concentrations of PDGF-BB in comparison to control (control: 1120.4 ± 157.4 N; 75 μ g: 1490.5 ± 224.5 N, $P = 0.029$; 150 μ g: 1486.6 ± 229.0 N, $P = 0.029$). Similarly, Ide et al.²³ found that FGF application in the tendon-bone junction during RCR was positively correlated to supraspinatus strength in rodent models 2 weeks following repair (control: 3.2 ± 0.6 N vs 100 mg/kg FGF-2 group: 6.6 ± 2.0 N, $P = 0.001$), and further, had higher tendon-to-bone insertion maturing scores as determined by system developed by Watkins et al.,²⁴ when compared to control (control: 10.6 ± 0.5 vs 100 mg/kg FGF-2 group: 15.8 ± 0.8 , < 0.002).

Technique

While techniques for harvesting PRP can vary depending on the system being used, the general principles are consistent. PRP for augmentation of RCR is obtained from drawing peripheral blood at the time of surgery. Notably, the peripheral blood must not be allowed to clot following the draw, as coagulation releases the essential growth factors stored in the platelet granules. Citrate may be added to bind ionized calcium and prevent coagulation. PRP is prepared via two broad methods: *centrifugation* or *apheresis*. Centrifugation allows the separation of blood components by density. From bottom to top, the layers are as follows: red blood cells, sediment, buffy coat, PRP, and increasing levels of pure plasma. Following removal of the plasma-rich portion and second centrifugation, typically the top-most 1 mL per 10 mL of blood will be collected as the PRP. Molecules such as calcium chloride, collagen, or bovine thrombin may then be used prior to injection to activate coagulation and thereby platelets.²⁵ Direct apheresis may also be used to directly extract PRP from other components of blood using manufacturer-prepared kits. For example, in one such kit,

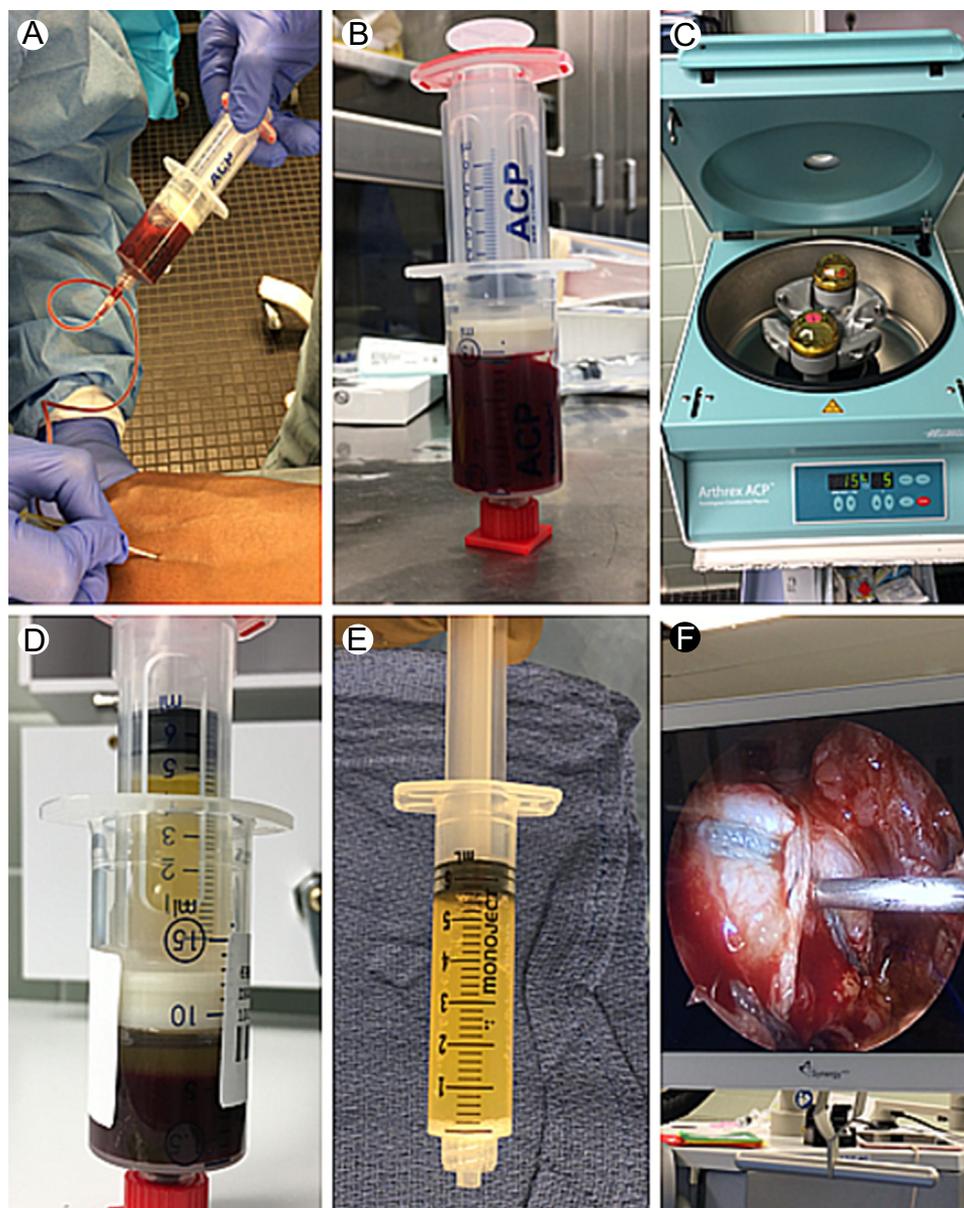


Figure 1 (A) Blood draw in the forearm. (B) Final draw of 15 mL of blood. (C) Centrifugation at 5000 rpm for 15 minutes. (D) Supernatant layer of platelet-rich plasma (top) and packed RBCs (bottom). (E) Extraction of only supernatant layer of PRP. (F) Injection into RCR repair site. (Color version of figure is available online.)

the clinician draws 15 mL of blood and mixes with Anti-coagulant Citrate Dextrose Solution (Solution A Citra Anti-coagulant, Inc., Braintree, MA, USA) for preparation of PRP into an Autologous Conditioned Plasma syringe (Arthrex, Inc; Naples, FL; Fig. 1). This is subsequently spun for 5 minutes at 1,500rpm in a centrifuge. The syringe itself is double lumen, which allows for extraction of the superficial platelet-rich layer into the second compartment of syringe following centrifuge. This layer of PRP is then injected into the site of interest, such as the RCR site.

PRP preparations can be sub-classified based on the actual preparation of the blood. Dohan et al. stratified PRP formulations by the following parameters: preparation kits and centrifuge, platelets and leukocytes, and fibrin.²⁶ This results in the following broad categories of PRP: pure platelet-rich

plasma (P-PRP), leukocyte and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), and leukocyte and platelet-rich fibrin (L-PRF). In addition, PRP can be described as leukocyte rich (LR-PRP) and leukocyte poor (LP-PRP).

The differences between leukocyte rich PRP and leukocyte poor PRP are not completely understood, especially with respect to treatment indications. Leukocytes are part of the buffy coat layer, which is often merged with the platelet-rich portion.²⁶ Since preparation protocols are not standardized, a given PRP preparation may or may not separate the buffy coat layer from the platelet-rich portion.^{27,28} An initial randomized controlled trial on double-row RCR by Zumstein et al. demonstrated that leukocyte rich platelet-rich fibrin was associated with significantly longer surgical time compared with leukocyte poor platelet-rich fibrin, but otherwise, there

Table 1 Randomized-controlled trials evaluating outcomes of PRP. ASES: American Shoulder and Elbow Society, UCLA: University of California at Los Angeles, SST: Simple Shoulder Test, SPADI: Shoulder Pain and Disability Index, VAS: Visual Analog Scale, SANE: Single Assessment Numeric Evaluation, ACD-A: Anticoagulant Citrate Dextrose Solution A.

Author/ Year	PRP Preparation	Sample Size	Type of Tear	Retear Rate (control vs PRP)	Relevant Findings
Jo (2013) ³⁸	Plateletpheresis system with leukoreduction. Normalized to platelet concentration and mixed with calcium gluconate	48	Large-Massive	55.6% vs 20.0% (p=0.023)	No difference in mean Constant, ASES, UCLA, SST, SPADI. Less reduction in muscle cross-sectional area in PRP group
Jo (2015) ³⁷	Plateletpheresis system with leukoreduction. Normalized to platelet concentration and mixed with calcium gluconate	74	Med-Large	20% vs 3% (p=0.032)	No difference in mean Constant, ASES, UCLA, SST, SPADI. Less reduction in muscle cross-sectional area in PRP group
Malavolta (2015) ³⁹	Apheresis set. 400mL blood; 5800rpm centrifuge for 15min; sodium citrate added; injection at bone-tendon interface: 10mL PRP, 1.5mL autologous thrombin, 0.8mL calcium chloride	54	Full thickness <3cm	18.5% vs 7.4% (p=0.42)	No difference in mean UCLA, Constant, VAS
Barber (2011) ³⁰	Cascade autologous platelet system. 18mL blood; centrifuge for 6min at 1,100 relative force; preloaded with calcium chloride, mixed, centrifuged at 1,450 relative force	40	Symptomatic rotator cuff tears 10-50mm in width	60% vs 30% (p=0.03)	No difference in mean ASES, SANE, SST, and Constant. Rowe score 84.8 (control) vs 94.9 (PRP) (p=0.03)
Randeli (2011) ⁴⁰	Apheresis set. 54mL blood with 6mL ACD-A; centrifuged at 3,200 RPM for 15 min; dispose platelet-poor and centrifuge again at 2,000RPM for 2 min	53	Full thickness rotator cuff tear	52% vs 40% (p=0.40)	Significantly greater SST (p=0.01), UCLA (p=0.03), Constant (p=0.006) scores, and strength in external rotation (p=0.004)
Pandey (2016) ⁴¹	Apheresis set. 50mL blood with citrate phosphate dextrose in 1:7 ratio; centrifuge for 12 min at 1500rpm	110	Medium or large-sized posterosuperior cuff tear	Med: 13% vs 4% (p=0.35) Large: 30% vs 4% (p=0.035)	Significantly greater VAS (p=0.057), Constant (p=0.008), and UCLA (p=0.002) scores at 12 months. No difference in ASES score (p=0.393)

ASES, American Shoulder and Elbow Society; SST, simple shoulder test; SPADI, shoulder pain and disability index; SANE, single assessment numeric evaluation; UCLA, University of California at Los Angeles; VAS: visual analog scale.

were no significant differences in clinical outcome, healing rate, or postoperative defect size as measured by imaging. Unfortunately, no specifications on preparation were described in their study.²⁹ An additional comparative series by Barber et al. used leukocyte poor platelet-rich plasma prepared using a commercial device with an inert polyester separator in addition to normal centrifugation during single row RCR. This study found postoperative tears via MRI in 60% of controls compared to 30% in the PRP-augmented group ($P = 0.03$); however, no differences in patient-reported outcomes were

found.³⁰ Gumina et al. found that the insertion of a platelet-leukocyte membrane between the rotator cuff tendon and its footprint in large full-thickness tears, improved rotator cuff integrity as measured from retear rates ($p=0.04$), but did not affect the change in functional outcomes. This was prepared by centrifuging 10mL of blood at $120 \times g$ (times gravity) for ten minutes, then adding calcium gluconate and batroxobin and centrifuging for 20-30min at $>1500 \times g$. The produced membranes were found to contain high concentrations of white blood cells and platelets.³¹

Table 2 Meta analyses evaluating outcomes of PRP. RR: Relative risk, ASES: American Shoulder and Elbow Society, UCLA: University of California at Los Angeles, SST: Simple Shoulder Test, VAS: Visual Analog Scale, SANE: Single Assessment Numeric Evaluation.

Author/Year	Articles	Keywords	Retear Rates (Control vs. PRP)	Relevant Findings
Warth (2015) ⁴²	8	Platelet rich plasma AND rotator cuff; PRP AND rotator cuff; fibrin matrix AND rotator cuff	36.7% vs. 28.7% ($p=0.21$)	No difference in ASES, UCLA, Constant, SST, VAS scores
Cai (2015) ⁴³	5	Platelet-rich plasma OR platelet gel OR platelet plasma OR PRP AND rotator cuff tear OR shoulder OR tendon	30.4% vs. 14.8% ($p=0.007$)	No difference in Constant, UCLA, SST, ASES Small-to-med size tears had difference in re-tear (control: 19.5% vs. PRP: 6.32%, $p=0.03$) but not large-to-massive (control: 64% vs. 41.4%, $p=0.55$)
Vavken (2015) ⁴⁴	13	Rotator AND platelet	RR: 0.87 all patients; no difference ($p=0.286$)	RR: 0.60 for small-med tears with difference PRP/control group ($p=0.038$) No differences in complications ($p=0.480$) Difference in effectiveness bw PRP and control was 0.0059 QALYs
Zhao (2015) ⁴⁵	8	Platelet-rich plasma, platelet, OR plasma and rotator cuff OR supraspinatus tendon	28% vs 26% ($p=0.66$) RR: 0.94; no difference	No differences between Constant ($p=0.66$) and UCLA ($p=0.32$) scores reported in studies

ASES, American Shoulder and Elbow Society; RR, relative risk; SST, simple shoulder test; SANE, single assessment numeric evaluation; UCLA, University of California at Los Angeles; VAS, visual analog scale.

Currently, there is no “standard” method of preparation for PRP in clinical trials. PRF is thought to provide a scaffold for which growth factors may be collected over a longer period of time than PRP.²⁹ Clinical studies comparing different forms of PRP concentrates have yet to be performed. Schär et al.³² found significantly more TGF- β 1 was released from L-PRF than L-PRP, but no differences in IGF-1 and PDGF-AB were found. PRF solutions also cannot be injected as they exist as a gel that must be applied to the area of interest. There are a few clinical trials that have examined the effect of PRF application in RCR, though none have found any improvement in structural and clinical outcomes compared to control.^{29,33-36}

Outcomes

Over the past decade, there has been increased attention to PRP in the setting of RCR, particularly given the prevalence of rotator cuff re-tear (Table 1). It is hypothesized that the addition of PRP to the repair construct improves the structural integrity of the repair, which is thought to be associated with improved clinical outcomes. Jo et al.³⁷ conducted a randomized control trial that demonstrated a significantly lower re-tear rate in patients with medium-to-large RCTs and PRP injected during surgery between their rotator cuff repair site and greater tuberosity at 1-year follow-up compared to nonblinded controls also undergoing arthroscopic repair (3% PRP vs 20% control, $P = 0.032$). PRP was prepared using a platelet-pheresis system 1 day before surgery, and concentration was

measured and normalized. They also found that the loss in cross-sectional area of the supraspinatus muscle, measured from MRI, at 1-year follow-up was 10-fold less in the PRP group when compared to the control group (PRP: -15.54 mm^2 control: -285.62 mm^2 , $P = 0.043$). The same group designed a similar study for large-to-massive RCTs, and again found that the PRP group had significantly lower re-tear rates (20% PRP group vs 55.6% control group, $P = 0.023$).³⁸ In this trial, the authors found no statistical difference in PROs, but did find an increase in overall function in the PRP group (8.44 ± 1.31 vs 7.21 ± 2.64 , $P = 0.043$) as determined by a custom survey that rates function on a 10-point scale.

In 2015, Malavolta et al. described their results from a randomized, double-blind study comparing patients with complete supraspinatus tendon tears (under 3 cm) undergoing arthroscopic RCR with PRP vs without (control). This group prepared PRP after anesthesia to ensure adequate blinding, by drawing 400 mL blood and centrifuging for 15 minutes at 5800 rpm. Autologous thrombin was prepared for activation using 10 mL of PRP and 0.4 mL of 10% calcium chloride. 40 mL PRP was injected at the tendon-to-bone interface during single row RCR. At an average 24-month follow-up, the authors found that both groups experienced increases in PROs compared to preoperative values, but that there were no statistical differences between the PRP and control groups. Further, there were no statistical differences in re-tear rates between the groups (control: 18.5% vs PRP: 7.4%, $P = 0.42$).³⁹

Meta-analyses on prospective trials provide a broader interpretation on the efficacy of PRP for augmentation of RCR (Table 2). Warth et al. examined eleven randomized prospective trials of PRP use, prepared with varying protocols of either commercial or manual centrifugation, in RCR that included both clinical outcomes as determined by PROs and structural outcomes as determined by imaging. Notably, the authors found that there were no statistically significant differences in ASES, Constant, SST, and VAS scores or overall re-tear rates (control: 36.7% vs PRP: 28.7%, $P > 0.05$). Interestingly, in medium-to-large tears, there was a decreased re-tear rate in patients that received PRP as diagnosed by imaging (57.1% control vs 25.9% PRP, $P = 0.046$).⁴² In a separate study, Cai et al.⁴³ analyzed 5 randomized controlled trials and found no statistically significant differences in PROs between both patients undergoing RCR with PRP vs without PRP augmentation, but found that the PRP group demonstrated 0.35 times the rate of re-tears (95% CI: 0.14-0.90, $P = 0.03$) in small-to-medium tendon tears. Preparation protocols varied between studies and largely consisted of either manual preparation with centrifugation or commercially available. All injections took place at the bone-tendon interface during either single-row or double-row repairs. No differences were found in patients with large-to-massive tears.

While PRP demonstrates some promise as a biologic augment to RCR, particularly with respect to structural outcomes, one barrier to its widespread clinical application is cost. The additional cost of using PRP comes from the costs associated with venipuncture, product preparation (either via centrifugation or prepared kit), and additional operating room time usage.⁴⁴ To better study the potential cost-effectiveness of PRP usage and preparation in the setting of RCR, Vavken et al. analyzed number needed to treat (NNT), complication rates, and quality-adjusted life years (QALYs) gained from prevention of re-tears. Under their model, the authors found if there was a reduction in re-tear rate by 40%, the NNT to reduce re-tears with PRP is 14. They concluded that PRP would only be cost effective if the total cost of PRP augmentation was less than \$652.11, while the authors estimated \$834 per PRP preparation.⁴⁴ Using a Markov Model to estimate the clinical benefit of PRP augmentation, Samuelson et al. estimated that PRP augmentation must report re-tear rates of no higher than 31% and be priced at \$270 to be cost-effective. From analysis of current literature, this requires an additional absolute risk reduction in re-tear rates of 9.1%.⁴⁶

Overall, additional research is still needed to determine the utility of PRP as a biologic augment for RCR, particularly with respect to clinical outcomes, cost-effectiveness, and preparation type.

Bone Marrow Aspirate Concentrate

Basic Science Background

Bone marrow aspirate concentrate (BMAC) is another biologic agent that has been used as an augment for patients undergoing RCR. The general concept behind BMAC involves

harvesting unspecialized cells, commonly referred to as “stem cells,” from the patient’s bone marrow, isolating and concentrating them to meet a certain threshold, and then implanting them at the site of interest to stimulate healing of the patient’s primary tissue.^{47,48} These cells possess a unique characteristic known as multipotency, which means that they are able to differentiate into a multitude of cell types with various specialized functions.⁴⁹ The cells harvested during BMAC procedures are multipotent adult stem cells that only have the capacity to differentiate into cells of the same germ layer. In this case, stem cells harvested from the bone marrow can differentiate to other tissue types of mesenchymal origin (eg, cartilage, tendon, bone, muscle)². The ability of these cells to differentiate into mesenchymal tissues, specifically tendon, is critical to the ability of BMAC to augment tendon healing following RCR.

The molecular changes associated with tendon degeneration highlight the clinical utility of BMAC, as MSCs are thought to be able to promote the production of type I collagen, improve the mechanical strength of tendon tissue, and improve the biology of the tendon-bone interface.^{47,50} Several in vitro studies utilizing both animal and human tissue samples have established the molecular mechanisms by which BMAC and MSC applications can help promote differentiation into appropriate tissues and improve tendon healing.^{1,2,8,9,13} Kim et al. used a rabbit model to analyze the impact of MSCs derived from the iliac crest 6 weeks after insertion into a full-thickness rotator cuff defect. The authors described evidence of cell viability after 6 weeks, as well as found that open-cell poly(lactic acid) scaffolds with MSCs incorporated before implantation showed significantly increased amounts of Type I collagen production compared to controls.¹ Yokoya et al.⁵⁰ demonstrated in rabbits that tibial MSCs implanted into a full-thickness rotator cuff defect resulted in increased amounts of type I collagen reorganization along the axis of the tendon, as well as substantial regeneration of tendon-bone insertion sites. Further, mechanical testing of the tendons displayed significantly stronger tissues in the group with implanted MSCs compared to controls.⁵⁰

Mazzocca et al.⁵¹ investigated the physiologic effects of various growth factors on tissue differentiation using MSCs obtained from the humeral head during arthroscopic rotator cuff repair. In this study, the authors exposed the harvested MSCs to various hormones and polypeptides including insulin, insulin-like growth factor 1 (IGF-1), β -fibroblastic growth factor (FGF- β), and growth differentiation factor 5 (GDF-5) in an effort to determine their capacities to differentiate into tendon tissue. Using various microscopic techniques, the authors found that MSCs treated with a one-time physiologic dose of 10^{-10} mol/L insulin showed significantly increased expression of tendon-specific markers type I and type III collagen, decorin, scleraxis, and tenascin C, compared to untreated control cells ($P < 0.05$).⁹ The MSCs treated with 10^{-10} -mol/L insulin also demonstrated increased levels of those tendon-specific markers compared to MSCs treated with growth factors IGF-1, FGF- β , and GDF-5 ($P < 0.05$).⁹ The authors concluded that the potential for one-time physiologic dosing of insulin to promote MSC differentiation into tendon



Figure 2 (A) Identification of anatomic landmarks—anterior superior iliac spine. (B) Aspiration of bone marrow. (C) Introduction of aspiration sample into angel system. (D) Angel system processing aspiration sample. (E) Production of bone marrow stem cell concentrate. (F) Bone marrow stem cell concentrate compared to original aspiration sample. (Color version of figure is available online.)

tissue may help develop efficient techniques for biologic augmentation of rotator cuff repair.⁹

Technique

Options for BMAC harvest include, but are not limited to, the iliac crest, proximal tibia, humeral head, and calcaneus. Unfortunately, there remains no consensus as to which donor site provides the highest yield of cells, is most efficient, or has the lowest amount of donor-site morbidity.^{48,50,52-55} An investigation by Utsunomiya et al.⁵⁶ compared cell yields, expandability, differentiation potential, and gene expression from MSCs derived from various soft tissues of the shoulder to determine the best potential source for RCR augmentation. They found that MSCs derived from synovial cells of the subacromial bursa had significantly higher yields and expandability than MSCs harvested from the joint synovium, supraspinatus tendon, or enthesis.⁵⁶ Mazzocca et al. demonstrated a successful technique using aspiration from a humerus suture anchor tunnel, centrifugation, isolation, purification, and re-extraction into a syringe that averaged about 10 minutes time, all done inside the operating room.⁴⁹ Other studies have described methods to harvest MSCs from peripheral blood.^{57,58} These findings bring into consideration the possibility that one extraction site may have

favorable outcomes compared to others, warranting further investigation.

Multiple commercial companies have designed bone marrow aspirate harvesting systems for clinical applications. For example, in one such kit, the clinician draws 60 mL of bone marrow aspirate for preparation of BMAC (Arthrex Angel System, Arthrex, Inc; Naples, FL; Fig. 2). For the authors' preferred technique, patients are placed under general anesthesia in the supine position, and their Anterior Superior Iliac Spine (ASIS) is identified and marked. The supine position is preferred because the ASIS becomes difficult to access in other surgical positions such as the beach chair. The injection site and surrounding area are then properly sterilized with either chlorhexidine or iodine. Using the ASIS as the anatomic landmark, an incision is made at the level of the ASIS and the trocar is introduced to a depth of 3 cm into the iliac crest. The stylet is removed and a 30-mL syringe is used to collect and discard the first 1 mL of aspirate to avoid the collection of bone or periosteum fragments. A new 30 mL syringe is used to collect the aspirate, rotating the syringe 90° while simultaneously aspirating in 2 mL intervals. The 30 mL of aspirate is then injected in to the Angel system for filtration. After the first 30 mL are collected, the process is repeated with another 30-mL syringe to obtain a total aspirate volume of 60 mL. If for some reason 60 mL of aspirate is unobtainable, the remaining

Table 3 Outcomes Following BMAC Augmenting RCR

Author/ Year	BMAC Preparation	Sample Size	Type of Tear	Postoperative Follow-Up	Relevant Findings
Gomes (2012) ⁵¹	100 mL marrow aspirated from posterior iliac crest in lateral recumbent position. Ficoll-Hypaque density gradient, resuspended in saline solution enriched with 10% autologous serum. Final volume 10 mL. Flow cytometry CD34, CD45, CD38 to confirm bone marrow origin	14	Full thickness	Minimum 12 mo	Mean UCLA score increased from 12 ± 3 to 31 ± 3.2 at 12 mo. MRI demonstrated tendon integrity in all (14/14) cases at 12 mo. No control group
Hernigou (2015) ⁵²	150 mL marrow aspirated anterior iliac crest in beach chair position. 3-5 perforations in iliac crest 2 cm apart to obtain aspirate. Mixed with citric acid, sodium citrate, dextrose solution. Isolated, purified, and concentrated in laboratory. Final volume 12 mL. Average 4300 ± 1800 MSCs/mL injected	90	Full-thickness supraspinatus (1.5-2.5 cm)	Minimum 10 y	100% (45/45) BMAC group healed by 6 mo vs 67% (30/45) control group. 87% (39/45) BMAC group intact rotator cuff at 10 y vs 44% (20/45) control group ($P < 0.05$). BMAC re-tear/no healing cases received fewer MSCs per cm^3 (1500 ± 1200 vs 4200 ± 1900 ; $P < 0.01$)
Mazzocca (2010) ⁵⁰	Intra-arthroscopic 14-gauge needle/60 mL syringe with 1 mL 1000 U heparin and 9 mL saline placed 25 mL into humerus medullary cortex at bone-cartilage junction of footprint. Suctioned 60 s. Sample placed on 17.5% sucrose gradient in 50 mL tube. Centrifuged 5 min at 205 g. MSC layer extracted with needle. FACS analysis CD73, CD90, CD45 to confirm stem cells	46	All rotator cuff tears necessitating arthroscopic repair	Mean BMAC group 10.6 ± 6.7 mo. Mean control group 10.0 ± 6.2 mo	No surgical complications or increased postoperative morbidity with BMAC. No significant difference in SANE score (BMAC 88.3 ± 10.5 ; control 83.6 ± 15.1 ; $P = 0.54$), range of motion (ext. rotation BMAC $65^\circ \pm 20.4^\circ$; Control $62.5^\circ \pm 17.1^\circ$; $P = 0.67$) (forward elevation BMAC $163^\circ \pm 30.6^\circ$; control $145.7^\circ \pm 41.4^\circ$; $P = 0.12$), or strength (BMAC median = 5, range: 4-5; control median = 5, range: 4-5; $P > 0.05$)

volume is collected from peripheral venous blood. The sample then undergoes centrifugation to isolate, purify, and concentrate the MSCs, which are injected into the rotator cuff defect during surgery. Although some research has shown that increasing concentrations of MSCs injected into the surgical site are associated with better clinical outcomes, no optimum concentration of MSCs has been established for augmentation of RCR.⁴²

While the findings from initial investigations and technological advancements are promising, there is no current gold standard regarding techniques for clinical application of BMAC. More research is needed to establish the efficacy, safety, and cost-effectiveness of optimal techniques to harvest and implant MSCs.

Outcomes

Several authors have described their experience with BMAC and RCR (Table 3). In 2012, Gomes et al. reported on 14 patients with full-thickness rotator cuff tears undergoing RCR with BMAC. In this series, the authors prepared saline suspensions of MSCs harvested from the patients' iliac crest and injected them into the tendon and bone after open RCR

utilizing a transdeltoid (lateral) approach.⁵³ Postoperative evaluation after 12 months demonstrated significantly increased UCLA scores compared to preoperative values. In addition, intact tendon integrity was confirmed by MRI in all patients after 12 months.⁵³ In 2014, Hernigou et al.⁵⁴ matched 45 patients undergoing arthroscopic RCR of full-thickness tears with BMAC harvested from the iliac crest to 45 control patients undergoing RCR without BMAC augmentation. Healing rates were analyzed postoperatively with ultrasound and MRI at 3 months, 6 months, 1 year, 2 years, and 10 years follow-up.⁵⁴ At the 6-month follow-up period, all 45 (100%) patients in the BMAC group demonstrated intact healing compared to 30 patients (66%) in the control group. At the 10-year follow-up period, 39 patients (87%) in the BMAC group were found to have intact tendon healing compared to 20 patients (44%) in the control group ($P < 0.05$). They also reported significant positive correlations between the number of MSCs implanted during the repair and tendon integrity at 10-year follow-up.⁵⁴ For the 6 patients that experienced no healing or re-tear in the BMAC group, there were significantly fewer MSCs per cubic centimeter (mean of 1500 ± 1200 vs 4200 ± 1900 ; $P < 0.01$) in the graft and a significant decrease in the average total number of progenitor cells ($14,000 \pm 9000$

vs 54,000 \pm 23,000; $P < 0.01$) than those patients who did not experience re-tear or no healing.

Overall, the available clinical data shows promising potential for BMAC to contribute to improved short- and medium-term outcomes following RCR.^{48,53,54,59} Importantly, and similar to the discussion on PRP, additional research is needed to determine the utility of BMAC as a biologic augment for RCR, particularly with respect to preparation technique and cost-effectiveness. Currently, there is no gold standard for BMAC procurement, method of application, or ideal amount/concentration of cells needed to promote tissue regeneration.⁴⁸ Although the study conducted by Hernigou et al.⁵⁴ found that higher cell concentrations were associated with better healing rates, more evidence must be obtained before clinical guidelines can be established. Mazzocca et al.⁵¹ experimented with alterations in the microenvironment of the MSCs using physiologic hormones, but additional studies are needed to confirm this practice as a viable, reproducible technique. Furthermore, there is still no clear consensus on the ideal anatomical site for harvesting of MSCs that poses the least risk to the patient while optimizing the number of viable cells acquired.^{52-54,56} Finally, there is a paucity of information available on the cost-effectiveness of BMAC as a biologic augment to RCR, and additional research is warranted.

Indications

Due to the minimal amount of conclusive data describing outcomes following RCR augmented with PRP, BMAC, or other biologics, it is difficult to determine true indications for adding biologic therapies to a standard RCR. Certainly, large-to-massive rotator cuff tears have the greatest predisposition to re-tear after repair. Biologic usage in these patients may be advantageous vs small-to-medium cuff tears; however, the literature has been inconsistent in demonstrating the effect of PRP in this population.^{37,38,44} In addition, clinical outcomes associated with these studies have not demonstrated much difference between PRP and control groups. Barriers to regular PRP use include the lack of standardized preparation technique, insufficient clinical information, and relatively high cost:benefit ratio. Further research of optimal administration of PRP may improve this. Larger clinical trials will also provide better information on specific indications for PRP use.

Given the paucity of literature regarding the clinical outcomes of RCR augmented with BMAC, no current indication exists for utilization of this technique in a clinical setting. Although initial pioneering investigations with both animal and human models have demonstrated that the potential for tendon regeneration, improved tendon integrity, and increased healing after BMAC augmentation may exist, the technology is still considered to be highly experimental and should not be included as part of any standard of care for rotator cuff repair based on available evidence.^{1,2,8,9,13,46,45} At this time, additional clinical trials utilizing BMAC augmentation in rotator cuff repair are recommended in order to establish a possible role in future patient treatment.

Summary

This review describes the utilization of biologic agents including PRP and BMAC during RCR, with an emphasis on technique and outcomes. Given the paucity of literature describing long-term outcomes with any biologic agent as an augmentation to RCR, additional research is needed to better understand the long-term impact of these agents.

References

1. Tempelhof S, Rupp S, Seil R: Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg* 8:296-299, 1999
2. Aleem AW, Brophy RH: Outcomes of rotator cuff surgery: What does the evidence tell us? *Clin Sports Med* 31:665-674, 2012
3. Varkey DT, Patterson BM, Creighton RA, et al: Initial medical management of rotator cuff tears: A demographic analysis of surgical and nonsurgical treatment in the United States Medicare population. *J Shoulder Elbow Surg* 25:e378-e385, 2016
4. Colvin AC, Egorova N, Harrison AK, et al: National trends in rotator cuff repair. *J Bone Joint Surg* 94:227, 2012
5. Galatz LM, Ball CM, Teefey SA, et al: The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. *J Bone Joint Surg* 86:219-224, 2004
6. Sugaya H, Maeda K, Matsuki K, et al: Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair: a prospective outcome study. *J Bone Joint Surg* 89:953-960, 2007
7. Sugaya H, Maeda K, Matsuki K, et al: Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: Single-row versus dual-row fixation. *Arthroscopy* 21:1307-1316, 2005
8. Hein J, Reilly JM, Chae J, et al: Retear rates after arthroscopic single-row, double-row, and suture bridge rotator cuff repair at a minimum of 1 year of imaging follow-up: A systematic review. *Arthroscopy* 31:2274-2281, 2015
9. Millett PJ, Warth RJ, Doman GJ, et al: Clinical and structural outcomes after arthroscopic single-row versus double-row rotator cuff repair: A systematic review and meta-analysis of level I randomized clinical trials. *J Shoulder Elbow Surg* 23:586-597, 2014
10. Sharma P, Maffulli N: Biology of tendon injury: Healing, modeling and remodeling. *J Musculoskelet Neuronal Interact* 6:181, 2006
11. James R, Kesturu G, Balian G, et al: Tendon: Biology, biomechanics, repair, growth factors, and evolving treatment options. *J Hand Surg* 33:102-112, 2008
12. Ziegler TR, Pierce GF, Herndon DN: Growth factors and wound healing: Basic science and potential clinical applications. Springer Science & Business Media,
13. Maffulli N, Ewen SW, Waterston SW, et al: Tenocytes from ruptured and tendinopathic Achilles tendons produce greater quantities of type III collagen than tenocytes from normal Achilles tendons. *Am J Sports Med* 28:499-505, 2000
14. Von der Mark K: Localization of collagen types. *Int Rev Connect Tissue Res*:265-324, 1981
15. Riley G, Harrall R, Constant C, et al: Tendon degeneration and chronic shoulder pain: Changes in the collagen composition of the human rotator cuff tendons in rotator cuff tendinitis. *Ann Rheum Dis* 53:359-366, 1994
16. Lubkowska A, Dolegowska B, Banfi G: Growth factor content in PRP and their applicability in medicine. *J Biol Regul Homeost Agents* 26:3S-22S, 2012
17. Marx RE: Platelet-rich plasma: Evidence to support its use. *J Oral Maxillofac Surg* 62:489-496, 2004
18. Senior RM, Griffin GL, Huang JS, et al: Chemotactic activity of platelet alpha granule proteins for fibroblasts. *J Cell Biol* 96:382-385, 1983
19. Hollinger JO, Hart CE, Hirsch SN, et al: Recombinant human platelet-derived growth factor: Biology and clinical applications. *J Bone Joint Surg* 90:48-54, 2008
20. Andia I, Sanchez M, Maffulli N: Tendon healing and platelet-rich plasma therapies. *Expert Opin Biol Ther* 10:1415-1426, 2010

21. Ferrari M, Zia S, Valbonesi M, et al: A new technique for hemodilution, preparation of autologous platelet-rich plasma and intraoperative blood salvage in cardiac surgery. *Int J Artif Organs* 10:47-50, 1987
22. Hee CK, Dines JS, Dines DM, et al: Augmentation of a rotator cuff suture repair using rhPDGF-BB and a type I bovine collagen matrix in an ovine model. *Am J Sports Med* 39:1630-1640, 2011
23. Ide J, Kikukawa K, Hirose J, et al: The effect of a local application of fibroblast growth factor-2 on tendon-to-bone remodeling in rats with acute injury and repair of the supraspinatus tendon. *J Shoulder Elbow Surg* 18:391-398, 2009
24. Watkins JP, Auer J, Gay S, et al: Healing of surgically created defects in the equine superficial digital flexor tendon: Collagen-type transformation and tissue morphologic reorganization. *Am J Vet Res* 46:2091-2096, 1985
25. Foster TE, Puskas BL, Mandelbaum BR, et al: Platelet-rich plasma: From basic science to clinical applications. *Am J Sports Med* 37:2259-2272, 2009
26. Ehrenfest DMD, Rasmusson L, Albrektsson T: Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). *Trends Biotechnol* 27:158-167, 2009
27. Everts PA, Knape JT, Weibrich G, et al: Platelet-rich plasma and platelet gel: A review. *J Extra Corpor Technol* 38:174, 2006
28. Everts PA, van Zundert A, Schonberger JP, et al: What do we use: Platelet-rich plasma or platelet-leukocyte gel? *J Biomed Mater Res A* 85:1135, 2008
29. Zumstein M, Rumian A, Thelu C, et al: Use of platelet-and leucocyte-rich fibrin (L-PRF) does not affect late rotator cuff tendon healing. A Prospective Randomized Controlled Study 2012
30. Barber FA, Hrnack SA, Snyder SJ, et al: Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. *Arthroscopy* 27:1029-1035, 2011
31. Gumina S, Campagna V, Ferrazza G, et al: Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. *JBSJ* 94:1345-1352, 2012
32. Schär MO, Diaz-Romero J, Kohl S, et al: Platelet-rich concentrates differentially release growth factors and induce cell migration in vitro. *Clin Orthop Relat Res* 473:1635-1643, 2015
33. Castricini R, Longo UG, De Benedetto M, et al: Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: A randomized controlled trial. *Am J Sports Med* 39:258-265, 2011
34. Rodeo SA, Delos D, Williams RJ, et al: The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: A prospective, randomized clinical study. *Am J Sports Med* 40:1234-1241, 2012
35. Bergeson AG, Tashjian RZ, Greis PE, Crim J, Stoddard GJ, Burks RT: Effects of platelet-rich fibrin matrix on repair integrity of at-risk rotator cuff tears. *The American journal of sports medicine* 40:286-293, 2012
36. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD: Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. *The American journal of sports medicine* 41:263-270, 2013
37. Jo CH, Shin JS, Shin WH, et al: Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: A randomized controlled trial. *Am J Sports Med* 43:2102-2110, 2015
38. Jo CH, Shin JS, Lee YG, et al: Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: A randomized, single-blind, parallel-group trial. *Am J Sports Med* 41:2240-2248, 2013
39. Malavolta EA, Gracitelli MEC, Ferreira Neto AA, et al: Platelet-rich plasma in rotator cuff repair: A prospective randomized study. *Am J Sports Med* 42:2446-2454, 2014
40. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P: Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *Journal of Shoulder and Elbow Surgery* 20:518-528, 2011
41. Pandey V, Bandi A, Madi S, et al: Does application of moderately concentrated platelet-rich plasma improve clinical and structural outcome after arthroscopic repair of medium-sized to large rotator cuff tear? A randomized controlled trial. *Journal of Shoulder and Elbow Surgery* 25:1312-1322, 2016
42. Warth RJ, Dorman GJ, James EW, et al: Clinical and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears with and without platelet-rich product supplementation: A meta-analysis and meta-regression. *Arthroscopy* 31:306-320, 2015
43. Cai Y-z, Zhang C, Lin X-j: Efficacy of platelet-rich plasma in arthroscopic repair of full-thickness rotator cuff tears: A meta-analysis. *J Shoulder Elbow Surg* 24:1852-1859, 2015
44. Vavken P, Sadoghi P, Palmer M, et al: Platelet-rich plasma reduces retear rates after arthroscopic repair of small-and medium-sized rotator cuff tears but is not cost-effective. *Am J Sports Med* 43:3071-3076, 2015
45. Zhao JG, Zhao L, Jiang YX, Wang ZL, Wang J, Zhang P: Platelet-rich plasma in arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 31:125-135, 2015
46. Samuelson EM, Odum SM, Fleischli JE: The cost-effectiveness of using platelet-rich plasma during rotator cuff repair: A Markov model analysis. *Arthroscopy* 32:1237-1244, 2016
47. Kim Y-S, Lee H-J, Ok J-H, et al: Survivorship of implanted bone marrow-derived mesenchymal stem cells in acute rotator cuff tear. *J Shoulder Elbow Surg* 22:1037-1045, 2013
48. Beitzel K, Solovyova O, Cote MP, et al: The future role of mesenchymal stem cells in the management of shoulder disorders. *Arthroscopy* 29:1702-1711, 2013
49. Dominici M, Le Blanc K, Mueller I, et al: Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytherapy* 8:315-317, 2006
50. Yokoya S, Mochizuki Y, Natsu K, et al: Rotator cuff regeneration using a bioabsorbable material with bone marrow-derived mesenchymal stem cells in a rabbit model. *Am J Sports Med* 40:1259-1268, 2012
51. Mazzocca AD, McCarthy MBR, Chowaniec D, et al: Bone marrow-derived mesenchymal stem cells obtained during arthroscopic rotator cuff repair surgery show potential for tendon cell differentiation after treatment with insulin. *Arthroscopy* 27:1459-1471, 2011
52. Mazzocca AD, McCarthy MBR, Chowaniec DM, et al: Rapid isolation of human stem cells (connective tissue progenitor cells) from the proximal humerus during arthroscopic rotator cuff surgery. *Am J Sports Med* 38:1438-1447, 2010
53. Gomes JLE, Da Silva RC, Silla LM, et al: Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. *Knee Surg Sports Traumatol Arthrosc* 20:373-377, 2012
54. Hernigou P, Lachaniette CHF, Delambre J, et al: Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. *Int Orthop* 38:1811-1818, 2014
55. Hyer CF, Berlet GC, Bussewitz BW, et al: Quantitative assessment of the yield of osteoblastic connective tissue progenitors in bone marrow aspirate from the iliac crest, tibia, and calcaneus. *J Bone Joint Surg Am* 95:1312-1316, 2013
56. Utsunomiya H, Uchida S, Sekiya I, et al: Isolation and characterization of human mesenchymal stem cells derived from shoulder tissues involved in rotator cuff tears. *Am J Sports Med* 41:657-668, 2013
57. Gianni AM, Siena S, Bregni M, et al: Granulocyte-macrophage colony-stimulating factor to harvest circulating haemopoietic stem cells for autotransplantation. *Lancet* 2:580-585, 1989
58. Siena S, Bregni M, Brando B, et al: Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: Enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 74:1905-1914, 1989
59. Kim SJ, Song DH, Park JW, et al: Effect of bone marrow aspirate concentrate-platelet-rich plasma on tendon-derived stem cells and rotator cuff tendon tear. *Cell Transplant* 26:867-878, 2017