Biologically Enhanced Healing of the Rotator Cuff

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Abstract: Failure of rotator cuff repair is a well-documented problem. Successful repair is impeded by muscle atrophy, fat infiltration, devascularization, and scar tissue formation throughout the fibrocartilagenous transition zone. This case study exemplifies a technique to biologically augment rotator cuff healing. Clinically, pain and function improved. Postoperative magnetic resonance imaging evaluation confirmed construct integrity. Biological enhancement of the healing process and physiologically based alterations in rehabilitation protocols can successfully treat complicated rotator cuff tears. Prospective studies with larger sample sizes and continued follow-up are necessary to assess the definitive efficacy of this treatment modality.

With more than 75,000 rotator cuff repairs performed each year and failure rates as high as 94%,1-8 it is well recognized that current surgical regimens need improvement. Rotator cuff tendons insert into bone through a specialized tissue comprising 4 distinct zones: tendon, nonmineralized fibrocartilage, mineralized fibrocartilage, and bone.9 For successful repair of the rotator cuff, the tendon must grow into the proximal bone of the humerus. Following surgical repair, the fibrocartilaginous transition zone becomes infiltrated with scar tissue.10-15 Unlike the normal transition zone, scar tissue cannot dissipate force, and the structural integrity of the zone is weakened, increasing susceptibility to tears.1-8 For this reason, many investigators have turned to biological augmentation to recreate a biomechanically equivalent layer of connective tissue.16-20

The combination of platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), and dermal allografts has the potential to aid in the repair of repetitively failed, full-thickness rotator cuff tears through biologic augmentation of the healing process and mechanical reinforcement. This article reviews the current literature pertaining to PRP, MSCs, and dermal allografts; provides a case study of a patient who underwent rotator cuff repair with the application of PRP, MSCs, and a dermal allograft; and explains how the appropriate environment and use of biological adjuvants can aid in the successful repair of recurrent rotator cuff tears.

Literature Review

Platelet-rich Plasma

Platelet-rich plasma is “a volume of plasma that has a platelet count above baseline.”21 Simplified, PRP comprises an increased concentration of platelets suspended in a small quantity of plasma. These platelets release a directly proportional quantity of cytokines, which are delivered to the injury to facilitate healing.22 Consequently, PRP has been promoted as a means to accelerate the biological healing cascade and optimize tissue repair and regeneration through the release of growth factors.

When activated, platelets release cytokines, such as platelet-derived growth factor,23 transforming growth factor-β,23 insulin-like growth...
factor-1 and -2,23 epidermal growth factor,23 vascular endothelial growth factor,23 and fibroblast growth factor.23 Recent research has confirmed that these bioactive molecules are capable of inducing angiogenesis and accelerating tendon healing.24,25

Despite the proven safety of PRP in the rotator cuff,16 the efficacy of PRP application during rotator cuff repair remains to be elucidated. The findings of Castricini et al19 suggest that PRP provides no clinical or structural advantage compared with traditional rotator cuff repair. Conversely, Barber et al26 reported that suturing 2 PRP fibrin matrices during rotator cuff repair reduced the incidence of re-tear rates and improved clinical outcomes. However, these discrepancies may be attributable to variations in PRP preparation. As PRP popularized, the heterogeneity of PRP in the heterogeneity of PRP in the rotator cuff,16,27,28,29,30,31 MSCs do not have an antigenic component, which allows allogenic MSCs to be applied without subsequent immunogenic reactions.

Bone marrow is the traditional source of human MSCs, but recently placental tissue has been studied as an alternative. Compared with bone marrow–derived MSCs, placenta-derived MSCs present with similar morphology, size, cell surface phenotype, characteristic MSC markers, and growth characteristics32,33 with no detection of the hematopoietic markers CD34, CD45, and HLA-DR.32,34,35 Furthermore, placenta-derived MSCs are capable of providing multipotent differentiation32,35 and possess beneficial immunosuppressive capabilities.32,35 In contrast with bone marrow derived MSCs, placenta-derived MSCs less readily differentiate into adipogenic cells, favor osteogenic differentiation, and consistently grow faster and more robustly.33 The characteristics of placenta-derived MSCs may advance tendon healing.

Mesenchymal Stem Cells

Mesenchymal stem cells are nonhematopoietic multipotent cells that differentiate into tissue-forming cell lineages, such as osteoblasts, adipocytes, chondrocytes, tenocytes, and myocytes.28,29 To date, no specific marker for stem cells has been isolated, although positive and negative markers have been identified. Positive markers include CD44, -73, -90, -105, -166 and STRO-1, whereas negative markers are CD34 and -45 and HLA-DR.30 It is important to note that CD45 is not only expressed on hematopoietic cells but is also required for T- and B-cell activation. In the absence of CD45 and MHC-II,30,31 MSCs do not have an antigenic component, which allows allogenic MSCs to be applied without subsequent immunogenic reactions.

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Mesenchymal stem cells improve tissue repair through 2 suggested mechanisms: direct differentiation and paracrine signaling. Although MSCs regenerate damaged tissue by differentiating into tenocytes, chondrocytes, and osteoblasts, paracrine signaling regulates the local cellular environment by releasing biologically active molecules, such as growth factors.

During the inflammatory and proliferative phases of wound healing, growth factors regulate cell migration, proliferation, differentiation, and matrix synthesis. Shortly after tendon damage, platelet-derived growth factor is produced, which has been shown to stimulate the production of additional growth factors and play a role in tissue remodeling.38 During the early inflammatory phase, insulin-like growth factor-1 and transforming growth factor-β increase activity. Increased expression of insulin-like growth factor-1 and transforming growth factor-β has been shown to aid in cellular migration and proliferation, which subsequently increases collagen production.39

Directly following the inflammatory phase, vascular endothelial growth factor is produced at its highest levels. At this time, both vascular endothelial growth factor and basic fibroblast growth factor potentially stimulate angiogenesis.40 Basic fibroblast growth factor regulates cellular migration and proliferation.40 With these dynamic properties, MSCs are ideal candidates to promote repair and healing. Given their potential to catalyze healing and tissue repair, MSCs have spiked an increasing interest.

Recent animal studies have demonstrated that MSCs can facilitate tendon healing.41-44 In rabbit Achilles tendon models, MSCs were shown to improve load and material properties through the reorganization of collagen fibers.42,45 Furthermore, in a rabbit anterior cruciate ligament model enhanced with MSCs, biomechanical and histological testing revealed restoration of normal cartilage histology and resulted in higher failure loads.43,44 However, only 1 known study has researched the use of MSCs to augment rotator cuff repair.46

As opposed to previous studies, MSC activity did not translate into improved biomechanical strength or organized cartilage structure and composition. However, the animals were only evaluated at 2 and 4 weeks, negating all long-term benefits. Encouragingly, Gulotta et al46 suggested that a combination of MSCs and mechanical reinforcement or growth factors may influence success rates.

Dermal Allografts

Dermal allografts are derived from human skin recovered from either live or cadaveric donation. Donor tissue screening and preparation processes are performed to meet the guidelines established by sources such as the American Association of Tissue Banks to reduce the risk of disease transmission and to minimize contamination and cross-contamination. Typically, allograft tissue undergoes serological and nucleic acid testing prior to release for transplantation. The skin is processed to remove cellular components to prevent host rejection while maintain-
ing the native biomechanical, biochemical, and collagen matrix structure. Lysis of cells, removal of cellular debris, and decontamination are essential to the process. The acellular nature of the tissue decreases the chances of immunogenic reactions.\(^{47}\) By retaining the natural collagen structure and mechanical properties, the final dermal allografts are designed to provide strength and serve as an extracellular matrix scaffold that allows for cell attachment, cell proliferation, and neovascularization for tissue remodeling.\(^{48,49}\) Despite the wide application of dermal allografts in areas such as general surgery and plastic and reconstructive surgery, few studies have investigated its use in rotator cuff repairs.\(^{49-52}\)

Preliminary studies confirmed the safety and effectiveness of dermal allograft application to augment human rotator cuff healing.\(^{50,51}\) Magnetic resonance imaging indicated full incorporation of the graft into native tissue.\(^{51}\) In a subsequent histological evaluation of a biopsy specimen obtained 3 months after rotator cuff augmentation with a human dermal scaffold, Snyder et al.\(^{49}\) reported cellular infiltration, alignment of collagen fibers, and blood vessel ingrowth. These results show that dermal allografts elicit histologic and morphologic remodeling in rotator cuff repair.

Barber et al.\(^{52}\) conducted a randomized, controlled trial to evaluate acellular human dermal matrix application to repair large (>3 cm) rotator cuff tears involving 2 tendons. Acellular human dermal allograft application resulted in a higher percentage of intact repairs. Presumably, rotator cuff repair coupled with biologic augmentation offers a safe and effective treatment for large and massive rotator cuff tears.

**Case Report**

**Clinical History**

In April 2011, a 54-year-old man presented to the outpatient clinic reporting pain in his right shoulder. His clinical history indicated that he underwent a rotator cuff repair of the right shoulder in March 2010, and, after a re-tear, a revision was performed in October 2010. Postoperatively, the patient reported continued right shoulder pain that increased with activity. On a scale of 1 to 10, reported pain was an 8 while moving and a 3.5 at rest. When subjectively evaluated, the patient rated the arm as only moderately functional (5 on a scale of 1 to 10).

In April 2011, a magnetic resonance arthrogram was ordered to rule out a repeat tear of the right shoulder, and findings were compatible with a full-thickness re-tear of the supraspinatus tendon (Figure 1A); 2.7 cm of the supraspinatus tendon was retracted. Moderate infraspinatus tendinopathy was noted. Both the supraspinatus and infraspinatus muscles had minimal atrophy. The biceps tendon was minimally subluxed into the intrasubstance delamination tears of the subscapularis tendon at the level of the mid to superior aspect of the bicipital groove. The intra-articular portion of the long head of the biceps tendon had moderate tendinopathy. Conservative and surgical management options were discussed with the patient, and risks and benefits were reviewed. The patient elected to undergo rotator cuff repair with PRP, MSCs, and a dermal allograft.

Informed written consent was obtained from the patient for photography used for scientific and educational purposes. His confidentiality and privacy were ensured and maintained. Data were abstracted into a coded and secure database.

**Procedure**

The patient received intravenous antibiotics and an interscalene block by the anesthesiologist. Following administration of general anesthesia, the patient was placed in the beach-chair position with the arm at 0° of abduction. The anesthesiologist drew 28 cc of blood from the patient. Eighteen cc of blood were spun down using a double centrifugation technique to form PRP. The Cascade autologous platelet system (Musculoskeletal Transplant Foundation, Edison, New Jersey) was used for PRP preparation. Platelet-rich plasma was prepared in accordance with previously described Musculoskeletal Transplant Foundation guidelines.\(^{53}\) The PRP and remaining 10 cc of whole blood were placed in separate sterile specimen cups.

After sterile preparation of the shoulder, an anterolateral incision was made following the previous rotator cuff repair incision. The deltoid musculature was bluntly separated.
but not detached from the acromion. All scar tissue in the subacromial and subdeltoid regions was lysed and excised. Sutures that had been placed were removed from the rotator cuff deficit. An acromioplasty was performed using a power burr and hand rasp. An adequate acromioclavicular decompression was performed.

Attention was then turned to the rotator cuff musculature and biceps tendon. Both the supraspinatus and infraspinatus muscles were torn (Figure 2A). Sharp lysis of adhesions was performed in the anterior, lateral, and posterior aspects of the shoulder. Meticulous mobilization of the supraspinatus and infraspinatus tendons occurred to return the tendons to their anatomic points of attachment under minimal rotator cuff tension.

Buried horizontal mattress FiberWire (Arthrex, Inc, Naples, Florida) sutures were placed from anterior to posterior to close the rotator cuff deficit and reapproximate the tendons to the greater tuberosity. Care was taken not to leave suture knots exposed on the bursal rotator cuff surface. The construct was anchored distally using multiple permanent anchors. The interdigitated suture fixation dispersed fixation stress over the majority of cuff insertion. The biceps tendon was left intact as a secondary point of rotator cuff suture fixation and stabilization.

**Application of Biologics**

A thick, dehydrated, 5×5×3 cm dermal allograft (Musculoskeletal Transplant Foundation) was reduced in size to 3×3 cm. The dehydrated allograft was reconstituted in PRP for 20 minutes. The chorionic membrane with MSCs (Graphix-Core membrane; Osiris Therapeutics, Inc, Columbia, Maryland) was reconstituted in sterile saline. The Graphix-Core membrane was then sutured to the subdermal side of the dermal allograft using absorbable sutures (Figure 2B).

Whole blood and PRP were placed on the bursal side of the rotator cuff repair. Permanent sutures were placed anterior and posterior to the glenoid. The dermal allograft–Graphix-Core membrane construct was carefully advanced over the proximal sutures and laid on top of the whole blood, PRP, and rotator cuff repair. The graft was tensioned to ensure optimal opposition to the cuff and anchored distally with 2 permanent sutures. The sides of the graft were sutured to the rotator cuff with absorbable horizontal mattress sutures. Horizontal mattress sutures were placed centrally on the graft to eliminate liftoff. Complete coverage of the rotator cuff deficit was achieved under minimal cuff tension with the arm at 0° of abduction (Figure 2C). No complications were encountered.

**Wound Closure**

The deltoid musculature was reapproximated and sutured with absorbable sutures, and the epidermis was reapproximated with subcuticular sutures and adhesive strips applied. The patient was returned to the supine position for extubation and then returned to the post-anesthesia care unit. The upper extremity was placed in a shoulder immobilizer with an abduction pillow.

**Rehabilitation**

Postoperatively, the patient was discharged with instructions for elbow, wrist, and hand range of motion (ROM) exercises. A follow-up appointment was scheduled for 5 days after discharge. At the first postoperative visit, the patient initiated pendulum exercises. This was continued for 3 weeks. After 3 weeks, the patient discontinued sling use. Throughout postoperative weeks 3 to 6, pendulum exercises, passive wall and table slides, isometrics, and...
gentle passive ROM were performed within the patient’s comfort zone. The patient was encouraged to obtain full forward flexion wall slides by 6 weeks postoperatively. During postoperative weeks 6 to 12, the patient continued passive slides and performed active assisted ROM and active ROM exercises. After 12 weeks, high-repetition, low-resistance rotator cuff and periscapular exercises began.

RESULTS
Objective and Subjective Assessments

One month postoperatively, the patient reported minimal pain (2.5 out of 10). At 9 months, the patient had full active forward flexion, 90° of abduction, and 90° of external rotation. At 90° of abduction, internal rotation was 80°. Active internal rotation was to the level of T12. The patient had regained normal use of the shoulder. Overall, the patient was satisfied with the outcome.

Clinical and MRI Evaluations

At 3, 6, and 9 months postoperatively, the right rotator cuff was reevaluated. At all 3 objective assessments, the right shoulder had no visible abnormalities: the surgical incision was clean, dry, and intact; the upper compartments were not swollen; and palpation of the right shoulder demonstrated no tenderness.

At 3 months, the right shoulder exhibited a wide ROM, painless motion in any direction, normal muscle tone, and no joint laxity. The 3-month MRI (Figure 1B) showed that the posterior margin of the infraspinatus tendon and the teres minor tendons were intact. The supraspinatus and infraspinatus muscles exhibited minimal atrophy. The graft–cuff construct remained intact.

At 6 months, the right shoulder exhibited flexion of 166°, active external rotation of 88°, internal rotation of 60°, and no joint laxity. The 6-month MRI (Figure 1C) confirmed the integrity of the graft–cuff construct. The supraspinatus and infraspinatus muscles exhibited minimal atrophy, but this was not significantly different from prior evaluations.

At 9 months, the patient reported continuous symptom improvement. The 9-month MRI (Figure 1D) indicated no appreciable tendon retraction. The intra-articular long head of the biceps tendon demonstrated mild tendinopathy without interval change. The teres minor was intact. No fluid signal intensity surrounded the anchors to suggest loosening. The supraspinatus and infraspinatus muscles were intact. No appreciable changes in the graft–cuff construct were noted.

DISCUSSION

The current article presented a novel technique to address the prevailing concern of rotator cuff repair failure.1–8 Following rotator cuff repair, the formation of scar tissue, impairment in vascularization, fatty infiltration, muscle atrophy, and intrinsic tendon degeneration impair the physiological healing process.9 The combination of PRP, MSCs, and a dermal allograft offer the potential to provide a structural support and scaffold to biologically augment the healing cascade.

Combining PRP, MSCs, and a dermal allograft promote tissue repair and regeneration. Platelet-rich plasma supplies a biologically enhanced concentration of platelets known to release a directly proportional quantity of growth factors,11 which are capable of inducing revascularization of soft tissue to improve and accelerate tendon healing.24,25 Mesenchymal stem cells not only regulate the local cellular environment by releasing biologically active molecules, but they also regenerate damaged tissue through differentiation into tenocytes, chondrocytes, and osteoblasts.28,29 The dermal allograft can serve as a biologic scaffold and provide mechanical reinforcement.49 The current authors’ findings suggest that the combination of these 3 biologics can create a structurally advantageous and biologically superior healing environment necessary for successful repair of recurrent rotator cuff tears. In comparison with traditional repair techniques, a secondary benefit appears to be a reduction in postoperative pain.

To successfully augment rotator cuff healing, the rehabilitation strategy must also optimize and maintain the local healing environment. Consequently, the rehabilitation protocol must allow for incorporation and capillary ingrowth of the dermal allograft while promoting the natural completion of the acute inflammatory phase of healing. This is necessary to avoid perpetuation into a chronic inflammatory phase, which may lead to tissue degradation. Additional consideration must be given to the temporal parameters of collagen formation and the process of fibrosis.

Integrity of the rotator cuff was evaluated by MRI at 3, 6, and 9 months postoperatively. Previous studies have shown that intact cuffs at 6 months postoperatively can predict long-term success.35 Pending no sports- or trauma-related events, the repair is expected to remain intact.35 Physical therapy was initiated following completion of the acute inflammatory phase of healing but before significant fibrotic changes occurred.45 This allowed for graft incorporation without the production of adhesive capsulitis or enzymatic tissue degradation. The biologic augmentation and rehabilitation strategy contributed to the successful repair of the rotator cuff tendon and restoration of a functional upper extremity.

This surgical technique offers a valuable socioeconomic option for complicated rotator cuff tears. Since the date of initial injury in October 2009, the patient underwent 3 rotator cuff repairs and extensive physical therapy over a 29-month timeframe. In addition to time lost and unemployment, a financial analysis revealed that the total charges amounted to >$200,000.
Initial identification of complex rotator cuff tears and surgical intervention with biologic enhancement may dramatically reduce the number of surgeries, and therapy sessions and overall socioeconomic cost. Most importantly, patients will resume activities of daily living more rapidly and return to work sooner.

CONCLUSION

This case study exemplifies the end result of the progressive use of dermal allografts, PRP, and MSCs. The combination of these biologic agents has been implemented in a dozen patients at the authors’ institution with recurrent rotator cuff tears. To date, no re-tears have been identified. In the future, the goal is to increase the sample size and report the histological conversion of the dermal allograft with MSCs and PRP to rotator cuff tissue.

The authors believe that this treatment modality offers an effective option for complicated, recurrent rotator cuff tears and is potentially an appropriate treatment for primary large and massive rotator cuff tears. Consistent with the return and production of more physiologic tissue and less scar tissue, this biologically enhanced repair may also assist the return of athletes to a high level of function. Ultimately, the cost of this biological enhancement will be effective in preventing the necessity for multiple surgeries, hospital expenditures, and rehabilitation sessions.

REFERENCES

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