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Platelet Rich Plasma in Rotator Cuff Repair

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Summary: Despite clinical success rates over 85%, persistent anatomic defects after rotator cuff repair are common and depend on the size of the tear repaired. The etiology of delayed or failed tendon to bone healing is multifactorial and biologic augmentation of a rotator cuff repair would be clinically desirable. Autogenous platelets contain many growth factors and are critical in the physiology of bone, soft tissue, and wound healing. Growth factors present in platelets include TGF-B, FGF, PDGF, EGF, and VEGF. Centrifugation techniques have been developed to create platelet rich plasma (PRP). These PRP preparations are designed to concentrate platelets and the growth factors they provide. PRP has been used to augment healing in various animal models as well as clinical situations in humans. This review examines the potential of using PRP to augment rotator cuff repair. **Key Words:** Rotator cuff repair—Platelet rich plasma—Tendon-bone healing.

Rotator cuff repair in the properly selected patient is a satisfying and successful operation for surgeon and patients alike, with clinical success rates averaging approximately 85%.[58] However, although several studies have correlated functional results after rotator cuff repair with postoperative integrity of the cuff,[24,54] the clinical success of rotator cuff repair does not always correlate with a healed rotator cuff.[6] Magnetic resonance imaging (MRI), arthrography, and ultrasound studies after rotator cuff repair have consistently revealed persistent defects in the supraspinatus tendon.[6] Despite improvements in techniques and development of shoulder specific instrumentation, a persistent anatomic defect in the rotator cuff after repair ranges from 20% to 54%, depending on the size of the tear repaired.[24,10,23,36] The rotator cuff is most often repaired with suture anchors or via sutures through bone tunnels to obtain firm approximation of the rotator cuff tendon tissue with the greater tuberosity via an open or arthroscopic approach. Although the greater tuberosity is frequently decorticated down to "bleeding bone" to augment healing, the re-tear rates after rotator cuff repair suggests that tendon to bone healing in this setting is suboptimal. The etiology of delayed or failed tendon to bone healing in this setting is likely multifactorial and could include factors such as fatigue failure of fixation devices (sutures or anchors), poor tendon tissue quality and vascularity, and delayed collagen fiber in-growth. Recent improvements in rotator cuff suture anchors and nonabsorbable sutures suggest that the pullout strength of the anchor, suture strength, and knot security are unlikely to fail before tissue failure.[9] This suggests that tendon tissue quality and tendon to bone healing is the likely failure point in rotator cuff repair. Therefore, delivery of growth factors or cells to augment tendon to bone healing is an attractive option to optimize rotator cuff healing. In this review, we evaluate the potential use of platelet rich plasma to augment tissue healing in the shoulder, in particular, the rotator cuff.

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CURRENT ROTATOR CUFF AUGMENTATION STRATEGIES

Because of the poor tissue quality often encountered in chronic or massive rotator cuff tears, the augmentation of rotator cuff repairs has long been a goal of orthopaedic surgeons. In the setting of poor tendon quality and to augment a tenuous repair, surgeons have used, with varying success: allograft tissue, autogenous biceps tendon and fascia lata, synthetic mesh, and extracellular matrices. Currently, one of the more common methods to augment tissue in rotator cuff repair is the use of extra-

cellular or synthetic matrices.[27] These matrices are commercially available and are derived from human or animal dermis, porcine small intestinal submucosa, equine pericardium, or bovine collagen. Some of the commercially available products in use for rotator cuff surgery are: GraftJacket (Wright Medical Technology, Arlington, TN) from human allograft skin; TissueMend (Stryker Orthopaedics, Mahwah, NJ) from fetal bovine dermis; Zimmer Collagen Repair Patch (Zimmer, Warsaw, IN) from porcine dermis; Pegasus Orthadapt (Pegasus Biologics, Irvine, CA) from equine pericardium; Cuffpatch (Arthrotek, Warsaw, IN) from porcine small intestinal submucosa; and Restore (DePuy, Warsaw, IN) from porcine small intestinal submucosa.[15] The biomechanical, biochemical, and cellular properties of these products were reviewed by Derwin et al.[15] The matrices have little inherent strength (an order of magnitude lower than canine infraspinatus) and some contain measurable amounts of DNA despite extensive processing. Despite initial success in animal models,[50] a recent review suggests that an inflammatory reaction can occur at the site of implantation. Valentin et al. tested 5 commercially available extracellular matrices (GraftJacket, Restore, TissueMend, Cuffpatch, and Zimmer Collagen Repair Patch) in a rat abdominal wall model and found a highly variable host response to each matrix, including acute or chronic inflammation.[55]

Clinical studies for most of these products are not available. Two clinical studies have been published evaluating porcine small intestinal submucosa as an augment for rotator cuff repair. A randomized trial and an MRI follow-up study in patients who underwent rotator cuff repair with the Restore (DePuy) porcine small intestinal submucosa patch suggest that these matrices offered little benefit and in some cases showed poor clinical results.[27,52] These poor clinical results could be associated with an inflammatory response to these materials observed by Valentin et al.[55] Clearly, the augmentation of rotator cuff repair deserves further study and is not yet clinically optimized. Establishing a method of delivering growth factors to improve the biology at the native tendon bone interface could be a potential alternative to current augmentation strategies.

BIOLOGY OF TENDON TO BONE HEALING

Compared with wound healing and fracture healing, tendon to bone healing is less well studied; the biology of tendon to bone healing is inherently different than these processes because it involves healing between two dissimilar tissues. After experimental repair of a tendon to bone, a cellular fibrovascular interface forms.[46,47] This response is likely mediated by undifferentiated cells from the bone and synovial cells.[29] A successful attachment site between tendon and bone is dependent on establishment of collagen fiber continuity between tendon and bone (Figs. 1 and 2). This connection between tendon and bone is initially the weak point of the construct after repair of rotator cuff and in tendon healing in bone tunnels.[13,46] If repaired tendon bone interfaces are tested to failure before establishment of the dense collagen interface (at least 8 weeks) the construct will fail at the interface. Experimental studies have shown that healing is initiated by tissue formation from the bone side rather than tendon.[47] Clearly, a biologic method to speed

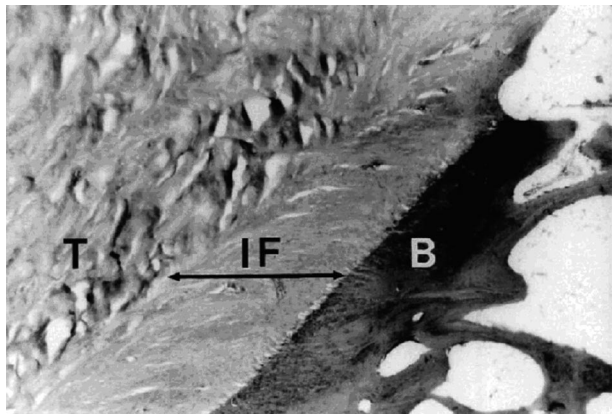

FIG. 1. Tendon bone healing in a dog tibia tunnel model at 26 weeks. Note the mature collagen fiber connection at the interface (IF) between tendon (T) and bone (B). (Reproduced with permission from: Rodeo SA, Arnoczky SP, Torzilli PA, et al. Tendon-healing in a bone tunnel. A biomechanical and histologic study in the dog. *J Bone Joint Surg Am* 1993;75:1795–1803.)

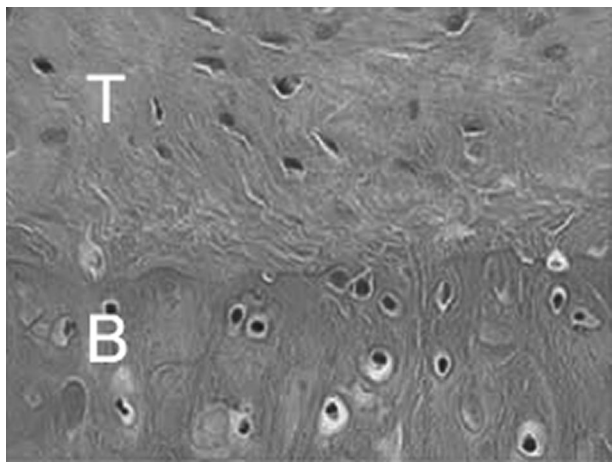

FIG. 2. Tendon (T) to bone (B) healing 8 weeks after rotator cuff repair in the rat. (Reproduced from: Cohen DB, Kawamura S, Ehteshami JR, et al. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. *Am J Sports Med* 2006;34:362–369.)

the formation of or increase the strength of the tendon-bone interface would be advantageous in the setting of rotator cuff repair.

Rodeo et al. and Anderson et al. has shown that tendon to bone healing can be augmented with application of exogenous osteogenic growth factors, including BMP-2.[1,47] In addition, it is know that growth factors, especially TGF-B, play an important role during the healing of supraspinatus tendons in an animal model.[20] In experimental rotator cuff repairs in rats, TGF-B-1 localized to repair tissue and corresponded with peak cellular proliferation. Enhancement of bone regeneration in orthopaedic surgery has become a reality with Food and Drug Administration (FDA) approval of recombinant BMP-2 and OP-1 for certain indications.[25] Autogenous fibrin clots are also a potential source for growth factors in orthopaedic surgery and have been used to aid in healing of both osteochondral defects and menisci in dogs.[4,42] An effective method of delivering autogenous growth factors to the site of rotator cuff repair could theoretically improve both the quality and velocity of tendon to bone healing.

PLATELET BIOLOGY

In addition to the critical role platelets play in coagulation and wound healing, platelets also are vital for bone healing. Platelets are derived from megakaryocytes that are found in bone marrow. Platelets do not have nuclei and circulate intravascularly for 10 days before being cleared by the spleen. Platelets contain α-granules that contain a multitude of important growth factors including, but not limited to, PDGF, TGF-B, VEGF, EGF, and IGF. Platelets collect at the site of endothelial injury and tissue injury and, on activation, release the growth factors that promote cell migration and differentiation at the site of injury. Activated platelets release these growth factors when the α-granules fuse with the plasma membrane. Platelets, therefore, provide an obvious and readily accessible source of autogenous growth factors. The important growth factors contained in platelets and their actions are summarized in Table 1.[18]

The abundance of growth factors contained in platelets led to an obvious clinical idea: can platelets be concentrated and delivered to promote wound healing. Improved centrifugation techniques have led to the ability to concentrate platelets as platelet rich plasma with the goal of delivering these concentrates as sources of growth factors to aid in healing. Growth factors derived from platelets play an essential role in fracture healing and bone repair;[7,35] therefore, there is potential for augmentation of rotator cuff healing with concentrated platelets and the growth factors they provide.

PLATELET RICH PLASMA

The normal concentration of platelets in human blood is between 150,000 and 400,000 platelets per mm ^{3}. Platelet rich plasma (PRP) is plasma that contains higher than physiologic platelet content.[37] On centrifugation of anticoagulated blood, three layers form: red blood cells (bottom); white blood cells/platelets (buffy coat) (middle); and plasma (top).[16] Although it is possible to produce PRP from units of whole blood, most surgical procedures require smaller amounts of PRP. Therefore, several companies have developed proprietary technol-

TABLE 1.
Growth Factors Present in Platelets

Growth factor	Function	References
Transforming growth factor-beta (TGF-B)	Stimulates undifferentiated mesenchymal cell proliferation, regulates endothelial, fibroblastic and osteoblastic mitogenesis; regulates collagen synthesis and collagenase secretion; regulates mitogenic effects of other growth factors; stimulates endothelial chemotaxis and angiogenesis; inhibits macrophage and lymphocyte proliferation	(5,44)
Basic fibroblast growth factor (bFGF)	Promotes growth and differentiation of chondrocytes and osteoblasts; mitogenic for mesenchymal stem cells, chondrocytes, and osteoblasts	(48,56)
Platelet derived growth factor (PDGF)	Mitogenic for mesenchymal stem cells and osteoblasts; stimulates chemotaxis and mitogenesis in fibroblast/glial/smooth muscle cells; regulates collagenase secretion and collagen synthesis; stimulates macrophage and neutrophil chemotaxis	(19,44)
Epidermal growth factor (EGF)	Stimulates endothelial chemotaxis/angiogenesis; regulates collagenase secretion; stimulates epithelial/mesenchymal mitogenesis	(11,53)
Vascular endothelial growth factor (VEGF)	Increases angiogenesis and vessel permeability; stimulates mitogenesis for endothelial cells	(35,43)
Connective tissue growth factor (CTGF)	Promotes angiogenesis, cartilage regeneration, fibrosis, and platelet adhesion	(26)

Modified with permission from Everts PA, Knape JT, Weibrich G, et al. Platelet-rich plasma and platelet gel: a review. *J Extra Corpor Technol* 2006;38:174–187.

ogy using small desktop centrifuges and smaller volumes of blood (45–60 mL) to produce between 5 and 10 mL of PRP. Several companies market their platelet concentration systems for orthopaedic surgeons: GPS II (Biomet, Warsaw, IN), Symphony II (DePuy), Cascade (Musculoskeletal Transplant Foundation, Edison, NJ), and Magellan (Medtronic, Minneapolis, MN). These systems consist of a reusable desktop centrifuge and single use blood collection and tube kits. Most systems rely on an initial low speed centrifugation to remove red blood cells followed by a higher speed centrifugation to concentrate platelets. The systems result in 2- to 8-fold increase in platelet concentration above physiologic levels.[16,17,30] Although they appear to use similar technology, these systems are different with respect to the anticoagulant used, final platelet concentration, platelet activation method, method of delivery, and level of growth factors released.[16,18,22] The most common method of platelet activation is by exposing the PRP to bovine or autologous thrombin, although some systems do not activate platelets at all before delivery.[16] Landesberg et al. demonstrated that many factors affect the platelet yield and therefore growth factor levels in PRP including: the type of anticoagulant, centrifugation speed and duration, and gel preparation method.[34] Given the variability in preparation methods for PRP, further study is clearly warranted to determine the optimal preparation method for orthopaedic applications of PRP. The individual surgeon must be aware of the preparation method and biologic profile of the PRP method he or she uses.

PRECLINICAL STUDIES USING PRP

In vitro studies have shown that PRP can cause osteoprogenitor cells to migrate and proliferate. Oprea et al. evaluated the effect of a 7-fold concentrate of platelets on rat osteoprogenitor cells derived from bone marrow on a fibrin gel.[41] PRP improved cell migration and recruitment in comparison to controls. Kanno et al. evaluated the effect of PRP on two osteoblast cell lines in vitro. PRP significantly improved the cell viability, differentiation, and alkaline phosphatase production of the cell lines.[28] Kilian et al. also demonstrated proliferation, migration, and differentiation toward an osteoblast lineage.[32] Lastly, this same group showed increased VEGF production and increased angiogenesis after implantation of PRP augmented hydroxyapatite paste in minipigs.[31] Increasing osteoprogenitor cell recruitment and activation and increased angiogenesis modulated by PRP could improve tendon/bone interface healing in rotator cuff repair.

When critically evaluating an animal study that attempts to delineate the osteoinductivity of a particular material, it is important to take several factors into consideration: the animal (immunocompetent or immunocompromised), the model (bone or skull defect), and the carrier.[21] All of these factors are important in determining if the study is clinically applicable. Evaluating the preclinical studies using PRP for orthopaedic applications adds another variable: the method of preparation and activation of the PRP. There have been many animal studies using PRP to augment bone repair, but results have been conflicting and carriers used in these studies have been highly variable. Secondly, many of the studies evaluating the in vivo effect of PRP on bone healing are in maxillofacial surgery literature and the applicability to orthopaedic surgery is uncertain. In an extensive review of the animal studies evaluating the effect of PRP on bone healing in the maxillofacial literature, Everts et al. concluded that only about half of the studies showed a positive result of PRP on bone healing. However, the methodology and activation of PRP was variable. Carriers and animal models also differ highly between studies.

There are only a few bone repair studies in orthopaedic literature evaluating PRP. Ranly et al. implanted human PRP or PDGF in combination with demineralized bone matrix (DBM) in the muscle of nude mice and found that the osteoinductivity of the DBM was reduced at all time points when PDGF or PRP was added.[45] These authors concluded that PRP could not be used to take an allograft of low osteoinductivity (DBM) and increase its osteoinductivity. This study, however, typifies the conundrum of interpreting the clinical relevancy of PRP animal research: the study involved a muscle model in an immunocompromised mouse and tested the effect of a combination of DBM and human PRP. The multitude of variables introduced by this study make it difficult to apply the findings to clinical practice. Dallari et al. evaluated PRP alone and in combination with freeze dried bone allograft and bone marrow cells in trabecular defects in rabbit femurs.[14] They found that the PRP alone inhibited bone formation, but in combination with bone marrow cells or allograft, increased bone healing was observed. This study demonstrates the importance of a carrier on the effects of PRP. Brodke et al. showed improved healing of dog femur defects treated with PRP enhanced DBM/allograft versus DBM allograft alone. These authors concluded that the combination of PRP/DBM/allograft was as effective as autograft in inducing healing.[8]

There are no published studies using PRP to augment healing at a tendon/bone interface. However, some recent studies show that PRP could have a beneficial effect

on tendon/ligament healing. First, Schnabel et al. showed that PRP enhances anabolic gene expression patterns in horse flexor tendons in vitro.[51] Expression of collagen 1, collagen 3, and COMP were all increased when the tendons were cultured in PRP. Second, Anitua et al. has shown that PRP increased proliferation/activity of cultured tendon cells and increased production of VEGF by the tendon cells.[2,3] Third, Murray et al. have published 2 large animal studies using a PRP collagen gel to improve healing of dog cruciate ligament defects and porcine cruciate ligament repairs.[39,40] Despite mixed results in animal studies leading to debatable efficacy, PRP technology has moved quickly to clinical studies in humans; the ease of obtaining PRP and the theoretical benign nature of concentrating a patient's own blood for a therapeutic purpose probably facilitated this transition.

CLINICAL STUDIES IN HUMANS

PRP has been used in many surgical settings including maxillofacial, cosmetic, cardiac, spine, orthopaedic, and for general wound healing. PRP has been used successfully in maxillofacial surgery in several studies (for review see[16,18]) including a randomized trial of 88 patients with mandibular defects treated with cancellous cellular marrow grafts with or without PRP.[38] Grafts with PRP showed twice the radiographic maturity at 6 months follow up. PRP has produced variable results in the spine literature. Carreon et al. reported on the results of a randomized clinical trial in posterior intertransverse lumbar spinal fusion surgery.[12] The authors prepared PRP using an 'autologous growth factor' filter (AGF filter; Biomet) and added the PRP to autogenous bone graft. The nonunion rate was 25% in the PRP group and 17% in the control group. Weiner and Walker reported on 32 patients receiving PRP prepared using AGF to augment posterior spinal fusions compared with 27 historical controls using a blinded method of radiologic scoring. The fusion rate for the control group was 24 of 27, or 91%. The fusion rate for the AGF group was 18 of 32 or 62%.[57] The authors of both spine fusion studies concluded that addition of PRP to iliac crest bone graft increased time and cost of surgery and possibly increased pseudarthrosis rates. However, Kevy and Jacobsen observed that PRP preparation using an AGF filter resulted in significant premature activation of platelets and[30] and Everts suggested that this application of a platelet 'releasate' may be responsible for the poor clinical results.[18] Small, non-controlled series by Savarino et al.[49] and Kitoh et al.[33] show that PRP can be used with efficacy to augment high tibial osteotomy and limb lengthening surgery, respectively. Lastly, PRP has been used successfully in foot an ankle surgery in three studies.[22] PRP has been used successfully to treat nonunions of the foot and ankle, to improve union in high-risk foot and ankle surgery, and to obtain syndesmotic fusion in total ankle arthroplasty.[22] Fortunately, safety of PRP technology has not been an issue and no oncologic or infectious complications have been reported.[18]

CONCLUSIONS AND FUTURE DIRECTIONS

Platelets represent an obvious source of bioactive growth factors that are easily concentrated at the bedside during surgical procedures using FDA approved, proprietary blood collection and centrifugation techniques. The efficacy of these PRP preparations is a controversial topic. Both clinical and animal studies, using variable preparation techniques have shown both success and failure. The optimal preparation and activation of PRPs as well as quantification of various growth factors in

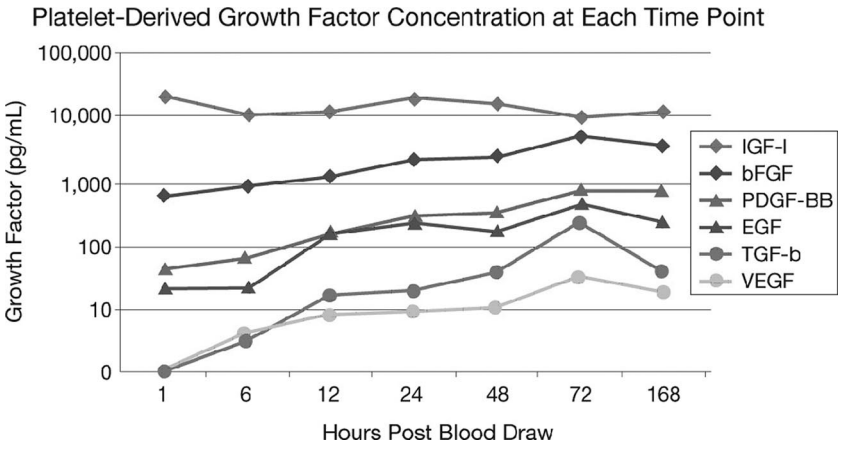

FIG. 3. Growth factor production of Cascade platelet rich fibrin matrix (PRFM) after second centrifugation measured over 7 days. Concentrations expressed as picograms per milliliter. Reproduced with permission from the Musculoskeletal Transplant Foundation.

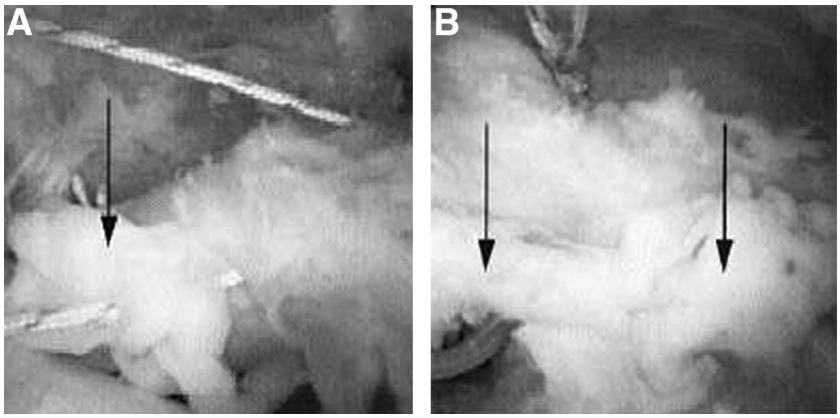

FIG. 4. Passage of the PRP implant is accomplished via an 8.25 mm clear cannula with the diaphragm removed. The implant is passed into the subacromial space using a suture (**A**) and the knots are tied, pinning the implant in the tendon bone interface above the suture anchor (**B**).

PRPs is unknown and deserves further study in vitro and in standardized, clinically applicable large and small animal studies. The fact that PRP is safe and prepared from autogenous blood may have allowed well-conducted clinical trials to proceed without optimizing the preparation of an ideal PRP in the laboratory first. Platelets and the growth factors they contain remain a relatively untapped resource in orthopaedic surgery with a potential for use in many areas, including rotator cuff surgery.

Currently at our institution we are conducting a randomized clinical trial of the efficacy of PRP prepared with the Cascade system from the Musculoskeletal Transplant Foundation (MTF) (Edison, NJ) in augmentation of arthroscopic rotator cuff repair. In clinical practice, 18 mL of blood is used to prepare approximately 4 mL of PRP. Two cycles of centrifugation are performed, the first in a separator tube and the second in calcium chloride at higher speed to produce a clot of platelets and fibrin that has enough density to hold a stitch. This clot is called Platelet Rich Fibrin Matrix (PRFM). The lack of excess thrombin prevents premature platelet degranulation and ensures platelet integrity during production. Most systems to produce PRP use $CaCl_2$ and thrombin to activate platelets. However, thrombin can lead to premature platelet activation and degranulation. This immediate release of cytokines can result in production of a platelet releasate rather than activated platelets. In unpublished data, flow cytometry of the PRFM reveals that platelets are intact and unactivated after PRP preparation and that active growth factors are released for at least 1 week (see Fig. 3, unpublished data, MTF, Edison NJ). Although these data need replication in peer reviewed literature and validation in animal studies, in vitro data using this method of PRP preparation is promising.

TECHNIQUE FOR USE OF PRP IN ROTATOR CUFF REPAIR

We perform rotator cuff repair in the beach chair position with the arm in an arm holder. After thorough bursectomy and subacromial decompression, mobilization of the tear is performed via the lateral portal using an electrocautery device, shaver, and periosteal elevator. After confirming that the tear can easily be reduced to the greater tuberosity, the tuberosity is gently decorticated using a shaver and 5.0 mm titanium screw-in suture anchors doubly loaded with #2 nonabsorbable sutures are placed. After placing and tying margin convergence sutures as necessary, a suture passer is used to pass simple or mattress sutures in the rotator cuff tendon from anterior to posterior via an 8.25 mm clear screw in cannula depending on tear configuration. All sutures are placed before tying. The diaphragm for the clear cannula is removed to allow passage of the PRP. A free needle is used to pass a limb of a simple suture from the anchor through the PRP and a knot pusher is used to deliver the PRP into the subacromial space (Fig. 4). The knot pusher is used to reduce the PRP to the anchor and sutures are tied so that the PRP is trapped in the tendon bone interface. Rehabilitation is unchanged from routine. The clinical and radiographic results of this trial will provide information about the potential for PRP augmentation of rotator cuff repair.

REFERENCES

1 Anderson K, Seneviratne AM, Izawa K, et al. Augmentation of tendon healing in an intraarticular bone tunnel with use of a bone growth factor. *Am J Sports Med* 2001;29:689–698.
2. Anitua E, Andia I, Sanchez M, et al. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. *J Orthop Res* 2005;23:281–286.
3. Anitua E, Sanchez M, Nurden AT, et al. Autologous fibrin matri-

ces: a potential source of biological mediators that modulate tendon cell activities. *J Biomed Mater Res A* 2006;77:285–293.
4. Arnoczky SP, Warren RF, Spivak JM. Meniscal repair using an exogenous fibrin clot. An experimental study in dogs. *J Bone Joint Surg Am* 1988;70:1209–1217.
5. Barnes GL, Kostenuik PJ, Gerstenfeld LC, et al. Growth factor regulation of fracture repair. *J Bone Miner Res* 1999;14:1805–1815.
6. Boileau P, Brassart N, Watkinson DJ, et al. Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? *J Bone Joint Surg Am.* 2005;87:1229–1240.
7. Bourque WT, Gross M, Hall BK. Expression of four growth factors during fracture repair. *Int J Dev Biol* 1993;37:573–579.
8. Brodke D, Pedrozo HA, Kapur TA, et al. Bone grafts prepared with selective cell retention technology heal canine segmental defects as effectively as autograft. *J Orthop Res* 2006;24:857–866.
9. Burkhart SS, Lo IK. Arthroscopic rotator cuff repair. *J Am Acad Orthop Surg* 2006;14:333–346.
10. Calvert PT, Packer NP, Stoker DJ, et al. Arthrography of the shoulder after operative repair of the torn rotator cuff. *J Bone Joint Surg Br* 1986;68:147–150.
11. Canalis E, McCarthy TL, Centrella M. Effects of platelet-derived growth factor on bone formation in vitro. *J Cell Physiol* 1989;140: 530–537.
12. Carreon LY, Glassman SD, Anekstein Y, et al. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. *Spine* 2005;30:E243,6; discussion E247.
13. Cohen DB, Kawamura S, Ehteshami JR, et al. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. *Am J Sports Med* 2006;34:362–369.
14. Dallari D, Fini M, Stagni C, et al. In vivo study on the healing of bone defects treated with bone marrow stromal cells, platelet-rich plasma, and freeze-dried bone allografts, alone and in combination. *J Orthop Res* 2006;24:877–888.
15. Derwin KA, Baker AR, Spragg RK, et al. Commercial extracellular matrix scaffolds for rotator cuff tendon repair. Biomechanical, biochemical, and cellular properties. *J Bone Joint Surg Am* 2006; 88:2665–2672.
16. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and applications in plastic surgery. *Plast Reconstr Surg* 2006;118:147e–159e.
17. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. *Plast Reconstr Surg* 2004;114:1502–1508.
18. Everts PA, Knape JT, Weibrich G, et al. Platelet-rich plasma and platelet gel: a review. *J Extra Corpor Technol* 2006;38:174–187.
19. Friesel RE, Maciag T. Molecular mechanisms of angiogenesis: fibroblast growth factor signal transduction. *FASEB J* 1995;9:919–925.
20. Galatz LM, Sandell LJ, Rothermich SY, et al. Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. *J Orthop Res* 2006;24:541–550.
21. Gamradt SC, Lieberman JR. Genetic modification of stem cells to enhance bone repair. *Ann Biomed Eng* 2005;32:136–147.
22. Gandhi A, Bibbo C, Pinzur M, et al. The role of platelet-rich plasma in foot and ankle surgery. *Foot Ankle Clin* 2005;10: 621,637, viii.
23. Gazielly DF, Gleyze P, Montagnon C. Functional and anatomical results after rotator cuff repair. *Clin Orthop Relat Res* 1994;(304):43–53.
24. Harryman DT , Mack LA, Wang KY, et al. Repairs of the rotator cuff. Correlation of functional results with integrity of the cuff. *J Bone Joint Surg Am* 1991;73:982–989.
25. Hidaka C, Cunningham ME, Rodeo SA, et al. Modern biologics used in orthopaedic surgery. *Curr Opin Rheumatol* 2006;18:74–79.
26. Hom DB, Maisel RH. Angiogenic growth factors: their effects and potential in soft tissue wound healing. *Ann Otol Rhinol Laryngol* 1992;101:349–354.
27. Iannotti JP, Codsi MJ, Kwon YW, et al. Porcine small intestine submucosa augmentation of surgical repair of chronic two–tendon rotator cuff tears. A randomized, controlled trial. *J Bone Joint Surg Am* 2006;88:1238–1244.
28. Kanno T, Takahashi T, Tsujisawa T, et al. Platelet-rich plasma enhances human osteoblast-like cell proliferation and differentiation. *J Oral Maxillofac Surg* 2005;63:362–369.
29. Kawamura S, Ying L, Kim HJ, et al. Macrophages accumulate in the early phase of tendon-bone healing. *J Orthop Res* 2005;23: 1425–1432.
30. Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. *J Extra Corpor Technol* 2004;36:28–35.
31. Kilian O, Alt V, Heiss C, et al. New blood vessel formation and expression of VEGF receptors after implantation of platelet growth factor-enriched biodegradable nanocrystalline hydroxyapatite. *Growth Factors* 2005;23:125–133.
32. Kilian O, Flesch I, Wenisch S, et al. Effects of platelet growth factors on human mesenchymal stem cells and human endothelial cells in vitro. *Eur J Med Res* 2004;9:337–344.
33. Kitoh H, Kitakoji T, Tsuchiya H, et al. Transplantation of culture expanded bone marrow cells and platelet rich plasma in distraction osteogenesis of the long bones. *Bone* 2007;40:522–528.
34. Landesberg R, Roy M, Glickman RS. Quantification of growth factor levels using a simplified method of platelet-rich plasma gel preparation. *J Oral Maxillofac Surg* 2000;58:297,300; discussion 300–301.
35. Lieberman JR, Daluiski A, Einhorn TA. The role of growth factors in the repair of bone. Biology and clinical applications. *J Bone Joint Surg Am* 2002;84-A:1032–1044.
36. Liu SH, Baker CL. Arthroscopically assisted rotator cuff repair: correlation of functional results with integrity of the cuff. *Arthroscopy* 1994;10:54–60.
37. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001;10:225–228.
38. Marx RE, Carlson ER, Eichstaedt RM, et al. Platelet-rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;85:638–646.
39. Murray MM, Spindler KP, Abreu E, et al. Collagen-platelet rich plasma hydrogel enhances primary repair of the porcine anterior cruciate ligament. *J Orthop Res* 2007;25:81–91.
40. Murray MM, Spindler KP, Devin C, et al. Use of a collagen-platelet rich plasma scaffold to stimulate healing of a central defect in the canine ACL. *J Orthop Res* 2006;24:820–830.
41. Oprea WE, Karp JM, Hosseini MM, et al. Effect of platelet releasate on bone cell migration and recruitment in vitro. *J Craniofac Surg* 2003;14:292–300.
42. Paletta GA, Arnoczky SP, Warren RF. The repair of osteochondral defects using an exogenous fibrin clot. An experimental study in dogs. *Am J Sports Med* 2992;20:725–731.
43. Peng H, Wright V, Usas A, et al. Synergistic enhancement of bone formation and healing by stem cell-expressed VEGF and bone morphogenetic protein-4. *J Clin Invest* 2002;110:751–759.
44. Pierce GF, Mustoe TA, Altrock BW, et al. Role of platelet-derived growth factor in wound healing. *J Cell Biochem* 1991;45:319–326.
45. Ranly DM, McMillan J, Keller T, et al. Platelet-derived growth factor inhibits demineralized bone matrix-induced intramuscular cartilage and bone formation. A study of immunocompromised mice. *J Bone Joint Surg Am* 2005;87:2052–2064.
46. Rodeo SA, Arnoczky SP, Torzilli PA, et al. Tendon-healing in a bone tunnel. A biomechanical and histological study in the dog. *J Bone Joint Surg Am* 1993;75:1795–1803.
47. Rodeo SA, Suzuki K, Deng XH, et al. Use of recombinant human bone morphogenetic protein-2 to enhance tendon healing in a bone tunnel. *Am J Sports Med* 1999;27:476–488.
48. Rosier RN, O'Keefe RJ, Hicks DG. The potential role of transforming growth factor beta in fracture healing. *Clin Orthop Relat Res* 1998;(355 suppl):S294–S300.
49. Savarino L, Cenni E, Tarabusi C, et al. Evaluation of bone healing enhancement by lyophilized bone grafts supplemented with platelet gel: a standardized methodology in patients with tibial osteotomy for genu varus. *J Biomed Mater Res B Appl Biomater* 2006;76:364–372.

50. Schlegel TF, Hawkins RJ, Lewis CW, et al. The effects of augmentation with Swine small intestine submucosa on tendon healing under tension: histologic and mechanical evaluations in sheep. *Am J Sports Med* 2006;34:275–280.
51. Schnabel LV, Mohammed HO, Miller BJ, et al. Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. *J Orthop Res* 2007;25: 230–240.
52. Sclamberg SG, Tibone JE, Itamura JM, et al. Six-month magnetic resonance imaging follow-up of large and massive rotator cuff repairs reinforced with porcine small intestinal submucosa. *J Shoulder Elbow Surg* 2004;13:538–541.
53. Steenfos HH. Growth factors and wound healing. *Scand J Plast Reconstr Surg Hand Surg* 1994;28:95–105.
54. Thomazeau H, Boukobza E, Morcet N, et al. Prediction of rotator cuff repair results by magnetic resonance imaging. *Clin Orthop Relat Res* 1997;(344):275–283.
55. Valentin JE, Badylak JS, McCabe GP, et al. Extracellular matrix bioscaffolds for orthopaedic applications. A comparative histologic study. *J Bone Joint Surg Am* 2006;88:2673–2686.
56. Wang JS. Basic fibroblast growth factor for stimulation of bone formation in osteoinductive or conductive implants. *Acta Orthop Scand Suppl* 1996;69:1–33.
57. Weiner BK, Walker M. Efficacy of autologous growth factors in lumbar intertransverse fusions. *Spine* 2003;28:1968,1970.
58. Williams GR Jr, Rockwood CA Jr, Bigliani LU, et al. Rotator cuff tears: why do we repair them? *J Bone Joint Surg Am* 2004;86-A: 2764–2776.