TITLE: Platelet-Rich Plasma Injection for Achilles Tendinopathy

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PLATELET-RICH PLASMA INJECTION FOR ACHILLES TENDINOPATHY

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of platelet-rich plasma injections for the treatment of chronic Achilles tendinopathy. This treatment has become increasingly popular among sports medicine physicians and has been chronicled in the popular press since high profile professional athletes such as Tiger Woods, Troy Polamalu and Hines Ward attested to the benefits of the therapy. In 2010, the first randomized trial of the therapy was published in the Journal of the American Medical Association.¹

BACKGROUND

Achilles tendon injuries

The Achilles tendon connects the muscles of the calf (gastrocnemius and soleus) to the heel bone (calcaneus). During exercise it may be subject to forces up to twelve times the person's body weight.² Achilles tendinopathy, previously called Achilles tendonitis, is a common injury in runners and other athletes. The diagnosis is based on symptoms of pain and swelling in the tendon that limits activities.³, ⁴ The diagnosis is usually separated into two distinct entities: insertional Achilles tendinopathy, which occurs within two cm. of the insertion of the tendon into the calcaneus and mid-portion Achilles tendinopathy, which occurs between two and six cm. proximal to the insertion of the tendon. The common sports injury is mid-portion tendinopathy and it will be the focus of this review.

Achilles tendinopathy is usually thought of as an overuse injury. Activities leading to Achilles tendinopathy include a rapid increase in running distance or speed, an increase in hill climbing, new running shoes, overpronation, and wearing high-heeled shoes.⁵, ⁶ Pain is typically felt in the middle of the tendon. After the initial injury, there is often morning stiffness and pain that may occur only when warming up or after exercise. These symptoms may progress over time to constant pain.

Achilles tendinopathy is common in runners accounting for approximately 11% of injuries. Tendons have a limited blood supply, which may contribute to poor healing following injury. Some estimate that as many as half of patients with Achilles tendinopathy are still symptomatic one year after the initial injury.
**Non-surgical treatment**

Rest, combined with icing and NSAIDS, is the usual initial treatment though there is limited evidence for efficacy of any of these interventions. Resting the injured tendon is thought to be an essential component of successful therapy, so encouraging the individual to switch to another activity, such as swimming or cycling, can help promote a sufficiently long rest period to allow healing to occur. A recent systematic review evaluated the clinical trial evidence supporting eccentric exercises, extra-corporeal shock wave therapy, concentric exercises, night splints, sclerosing injections, topical glycerol nitrate, and corticosteroid injections for the treatment of Achilles tendinopathy. The strongest evidence for efficacy was for eccentric exercises with conflicting evidence for the other treatment modalities. Eccentric exercises combine stretching with contraction of the muscles. For Achilles tendinopathy, this usually involves standing on a step and slowly lowering the heel. The number of repetitions and the load applied to the Achilles tendon is increased gradually over weeks.

**Platelet-rich plasma (PRP)**

The use of PRP grows out of long-standing research into how to harness growth factors to promote healing. Platelets contain packets of growth factors called alpha granules. The growth factors in alpha granules include platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factors I and II, and fibroblast growth factor. These factors promote the formation of extracellular matrix, granulation tissue, epithelial tissue as well as stimulating cell growth and proliferation, angiogenesis, and cell migration. The hope is that coordinated use of these growth factors will accelerate the removal of necrotic tissue and speed tissue regeneration and healing.

The normal concentration of platelets is approximately 200,000 per microliter. The goal of devices used to produce PRP is to raise the concentration to at least 1 million platelets per microliter – the threshold that is felt to be clinically active. To produce PRP, anticoagulated blood is centrifuged to separate red and white blood cells from the platelet and plasma and to separate the plasma into platelet-rich and platelet-poor fractions.

There are several approaches to trigger the release of the growth factors from the PRP. Some systems add bovine thrombin to activate clotting, though concerns have been raised about immune reactions to the bovine thrombin. This approach leads to rapid release of the growth factors. Another uses calcium chloride, which creates a fibrin gel that traps platelets and releases growth factors over approximately seven days. A third system uses type I collagen to activate the platelets and to create a collagen gel. Finally, the PRP can be directly injected and allow the patient’s own collagen to activate the platelets. In all cases, the patient’s
own blood is the source for the PRP.

PRP has been promoted for use in non-healing tendon injuries, acute tendon injuries, muscle and ligament strains, osteoarthritis, articular cartilage injury, diabetic wound healing, bone fracture healing, and spinal fusion. The editor of the American Journal of Sports Medicine coined the phrase “platelet-rich panacea” to describe the current enthusiasm for PRP.11 Most articles have minimized the harms of PRP, but concerns have been raised about the potential for excessive growth, delays in tissue remodeling, and excessive scarring.12

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The injection of PRP is a procedure and therefore not regulated by the US Food and Drug Administration (FDA).

The FDA has approved multiple devices used to separate whole blood into PRP through the 510(k) process.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “platelet rich plasma,” “PRP,” “platelet gel,” “platelet concentrate,” or “platelet releasate.” The results were crossed with the results from a search on “Achilles tendon,” “tendo Achilles,” “Achilles,” “tendinopathy,” “tendinosis,” “tendonitis,” or “tenosynovitis.” The search was performed for the period from 1966 through September 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the essential patient oriented outcomes: pain, activity level, and return to pre-injury function.

The search identified 116 potentially relevant trials. After elimination of duplicate and non-relevant
references including animal model studies in rats and rabbits, three articles were reviewed in full. These three references included one case report using PRP to treat a patient with a partial tear of the Achilles tendon\textsuperscript{13}, one case series of 14 patients in Poland\textsuperscript{14}, and one randomized trial.\textsuperscript{1}

**Level of Evidence: 1 and 5.**

**TA Criterion 2 is met.**

**TA Criterion 3:** The technology must improve net health outcomes.

There are several well-validated scales that are commonly used to evaluate response to therapy for Achilles tendinopathy. The Victorian Institute of Sports Assessment – Achilles (VISA-A) questionnaire measures both pain and activity on a 100-point scale with a score of 0 representing maximal pain and no activity and 100 representing maximal activity with no pain. The American Orthopedic Foot and Ankle Society (AOFAS) hindfoot scale sums a possible 40 points for pain, 50 points for function, and 10 points for alignment. Patient assessment comprises 70 points with the remaining 30 points based on physician assessment of function and alignment. Higher scores represent less pain and greater function. Pain may also be assessed directly using a ten-point visual analog scale (VAS) with zero indicating no pain and ten indicating the worst possible pain.

**Case Series**

There is one case report from Italy describing treatment of a partial tear of the Achilles tendon.\textsuperscript{13} Surgery is the most common treatment option for a partial tear of the Achilles tendon. In this case a 34-year-old competitive athlete was treated with three PRP injections into the region of the tear at one week intervals. After a rehabilitation program, the patient was able to play for 20 minutes in a basketball game 64 days after the injury and in a full game at 75 days. Eighteen months later, he has required no further treatment and continues to play competitively. The authors suggest that platelet growth factors may have promoted rapid tendon healing.

The second study prospectively collected data on 14 patients with non-insertional Achilles tendinopathy. One patient was injected in both tendons. The study assessed the VISA-A scale and the AOFAS hindfoot scale prior to treatment and after three, six, and 18 months of follow-up. The average score on the VISA-A scale improved from 24 points to 96 points ($p = 0.00066$) and the average score on the AOFAS hindfoot scale improved from 55 points to 96 points ($p = 0.00066$) at 18 months. There were clearly significant
improvements for these 14 patients, but it is unclear if this represents the natural history of recovery from Achilles tendinopathy, the effect of other co-interventions used to treat these patients or a true biological effect of the PRP injection. The results from these case series are encouraging, but require confirmation in a randomized trial.

**Randomized trial**

There is one published randomized trial investigating the value of PRP for the treatment of chronic midportion Achilles tendinopathy at a single sports medicine clinic in Holland. Patients between the ages of 18 and 70 years with at least two months of symptoms and a clinical diagnosis of Achilles tendinopathy based on a painful, thickened Achilles tendon between two and seven cm proximal to the insertion of the tendon into the calcaneus were eligible for randomization. Patients with insertional disorders, tendon rupture, prior PRP injection therapy, or prior eccentric load therapy were excluded from randomization.

PRP was prepared according to the manufacturer’s instructions using six mL of blood mixed with six mL of citrate to prevent clotting. PRP was separated from the remainder of the blood after 15 minutes of centrifuging. One mL of PRP was kept for evaluation of potential contamination. Four mL of PRP and four mL of a saline injection were prepared in identical syringes for every patient. The study maintained blinding of the treating sports medicine physician, the patients, and the researchers. The treating physician injected 2 cc of local anesthetic in the subcutaneous tissue and then ultrasound was used to guide the injection of the blinded fluid in 15 separate depots in the degenerative portion of the Achilles tendon. All patients followed the same rehabilitation program after the injection. Only short walks were permitted during the first two days. Then, walks up to 30 minutes through day seven. During the second week stretching exercises were started followed by twelve weeks of an eccentric exercise program. The primary outcome measure was change in the VISA-A score. Secondary outcomes included patient satisfaction and return to sports.

The study randomized 54 patients: 27 to the PRP injection group and 27 to the saline placebo group. There were no patients lost to follow-up and data was 100% complete in both groups. The baseline characteristics of the two groups were similar. Their average age was 50 years and 52% were female. There was a trend towards greater symptom duration in the PRP group (36 weeks versus 26 weeks, p NR). The VISA-A score at 24 weeks had improved significantly from baseline in both groups, but there were no differences between the two groups (+21.7 in the PRP group versus +20.5 points in the saline injection group, p NS). The baseline VISA-A score and the duration of symptoms were associated with the primary outcome measure (p<0.05 for both). In multivariable models adjusting for both covariates, injection with PRP was still not associated with the change in the VISA-A score at 6, 12, or 24 weeks. For example, the adjusted between group difference at 24 weeks favored the saline injection arm by 0.9 points (95% CI -12.4 to 10.6 with
negative numbers favoring the saline injection group). There were no significant differences on any of the secondary outcomes either. Patient satisfaction at 24 months was good or excellent for 56% of patients in the PRP group and 63% of patients in the placebo group (adjusted difference -4.1%, 95% CI -26 to 18%). The percentage of participants who had returned to their desired sport at 24 weeks was 78% in the PRP group and 67% of patients in the placebo group (adjusted difference 11%, 95% CI -17 to 20%). There was no bacterial growth in the samples of PRP and no complications from the therapy.

This study was a good quality randomized trial. There was excellent allocation concealment, complete blinding, 100% follow-up, completely equivalent co-interventions and an intention to treat analysis without any concerns for cross-over and non-receipt of treatment as randomized. The primary concern is that the trial was relatively small and thus underpowered to detect small effects. There were also baseline imbalances in some covariates that had the potential to have an impact on the final results. However, analyses accounting for the baseline imbalances did not change the outcome. For the primary outcome and most of the secondary outcomes, there were no trends that favored PRP over placebo injections. Some investigators believe that the trauma induced by introducing a needle into the affected area may be a stimulus for healing. Thus the placebo group may have benefited from the saline injections. This concern does not offer any support for PRP therapy. The co-intervention of eccentric exercises may have obscured any benefit of PRP, though the trial provides evidence that PRP offers no additional benefit beyond eccentric exercise. There may still be benefit in patients who have failed an adequate trial of eccentric exercise or who are unable to perform the exercises, though this should be tested in a clinical trial before the therapy is widely applied.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established alternative for Achilles tendinopathy is eccentric exercises – stretching the tendon while simultaneously contracting the calf muscles (gastrocnemius and soleus). The randomized trial described above used eccentric exercise with a placebo injection as the appropriate comparator. There were no benefits to patients in the PRP injection group in terms of pain reduction, patient satisfaction, improvements in activity level and return to sports.

TA Criterion 4 is not met.
TA Criterion 5: The improvement must be attainable outside of the investigational setting.

To date, clear improvements in patient outcomes compared with standard rehabilitation have not been demonstrated in or out of the investigational setting.

TA Criterion 5 is not met.

CONCLUSION

Overuse injuries of the Achilles tendon are common, particularly among runners. Many patients’ injuries can be managed conservatively, but recovery is often slow and prolonged. The limited blood supply to the tendon may contribute to slow or stalled healing. The growth factors in PRP are hypothesized to jump start the healing process for patients with chronic Achilles tendinopathy.

One case report highlighted the rapid recovery of a competitive athlete from a partial tear of the Achilles tendon that was treated with PRP injections. Additionally, one case series of 14 patients with mid-portion Achilles tendinopathy reported dramatic improvements on two validated scales of Achilles tendon pain and function within three months of therapy and sustained through eighteen months. No significant complications were reported.

However the one high quality, double-blinded, sham-controlled randomized trial found no benefit to PRP injections compared with sham injections. The trial was relatively small, so it may have been underpowered to detect small improvements from PRP injection. There are also alternative approaches to processing and activating PRP. It may be that the approach used in this trial was not effective, but other approaches will be effective. However, based on the current evidence, PRP injection, added to the standard eccentric exercise therapy, does not appear to be an effective approach to the treatment of Achilles tendinopathy. A search of ClinicalTrials.gov indicates that there are at least 41 trials testing PRP for a variety of musculoskeletal and orthopedic conditions, so more data should be available in the near future.

RECOMMENDATION

It is recommended that use of platelet-rich plasma injections for the treatment of non-insertional Achilles tendinopathy does not meet CTAF TA Criterion 3 through 5 for improvement in health outcomes.
October 13, 2010

This is the first review of this technology by the California Technology Assessment Forum

*The CTAF panel voted to accept the recommendation as presented.*
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) has not conducted an assessment of this technology.

Centers for Medicare and Medicaid Services (CMS)

CMS does not have a National Coverage Determination for the use of PRP for tendinopathies.

California Orthopaedic Association (COA)

The COA noted that they agree with the recommendation and that more studies are needed to evaluate this technology.

American Academy of Orthopedic Surgeons (AAOS)

The AAOS was invited to provide an opinion and to have a representative provide testimony at the meeting.

California Podiatric Medical Association (CPMA)

The CPMA was invited to provide an opinion and to have a representative provide testimony at the meeting.

American Orthopedic Foot and Ankle Surgeons (AOFAS)

Patient education was found on the AOFAS web site regarding Achilles Tendonitis. It does not mention the use of PRP.

### ABBREVIATIONS

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<tr>
<td>CTAF</td>
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<td>PRP</td>
<td>Platelet-rich Plasma</td>
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<td>FDA</td>
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REFERENCES


