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Therapeutic efficacy of platelet-rich plasma injections in treating high hamstring tendinopathy

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Thesis

THERAPEUTIC EFFICACY OF PLATELET-RICH PLASMA INJECTIONS IN TREATING HIGH HAMSTRING TENDINOPATHY

by

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B.A., University of California, Berkeley, 2010

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2013
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HAMSTRING MUSCLE AND TENDON INJURIES ARE COMMONLY SEEN IN SPORTS MEDICINE
CLINICS, ESPECIALLY IN TRACK AND FIELD ATHLETES. HOWEVER, A LESS COMMON SUBSET OF
THOSE INJURIES HAS RECENTLY BEGUN TO GAIN MORE ATTENTION AMONG RESEARCHERS AND
CLINICIANS AND IS REFERRED TO AS HIGH HAMSTRING TENDINOPATHY. PATIENTS SUFFERING
FROM THIS CONDITION TYPICALLY REPORT DEEP BUTTOCK PAIN BROUGHT ON BY RUNNING, OR
IN SEVERE CASES EVEN BY PROLONGED SITTING, SUCH AS IN DRIVING A CAR FOR LONG
PERIODS OF TIME. DIAGNOSIS OF THIS CONDITION REQUIRES A SPECIFIC PATIENT HISTORY,
POSITIVE SIGNS ON PHYSICAL EXAMS, AS WELL AS POSITIVE FINDINGS ON IMAGING STUDIES,
PRIMARILY MRI AND ULTRASOUND. TREATMENT FOR HIGH HAMSTRING TENDINOPATHY
TYPICALLY STARTS WITH CONSERVATIVE MEASURES FOR PAIN MANAGEMENT INCLUDING ICE,
ELECTRICAL STIMULATION, AND PULSED ULTRASOUND. AS SOON AS PATIENTS ARE ABLE, A
PHYSICAL THERAPY PROTOCOL IS PRESCRIBED INVOLVING STRETCHING, ALONG WITH
strengthening, progressing to eccentric exercises. In cases where symptoms are persistent, more aggressive treatments can be followed, such as corticosteroid injections, extracorporeal shockwave therapy, and surgery in more severe cases. However, because these therapies are often ineffective, expensive, and potentially carry high risks, physicians have begun to turn to alternative forms of therapy. One such treatment gaining recent popularity is the use of platelet-rich plasma injections (PRP).

The widely held belief is that PRP provides a higher than average concentration of growth factors than is normally contained in platelets and that these stimulate the wound healing cascade and help in tissue repair and regeneration. PRP is prepared using autologous whole blood from patients by two rounds of centrifugation, separating and concentrating the platelets from other components such as red blood cells and leukocytes.

Although PRP has shown potential in treating musculoskeletal injuries such as chronic patellar tendinosis and chronic elbow tendinosis there has only been one study mentioning the injection of PRP for treating chronic high hamstring tendinopathy. This paper seeks to investigate the therapeutic efficacy of PRP in
treat these injuries by following the progress of patients receiving PRP injections over a 12-week period. Subjects were selected using specific inclusion and exclusion criteria from patients electing to receive the treatment. After providing informed consent, patients were evaluated using a baseline evaluation form and Lower Extremity Functional Scale questionnaire before receiving a single, ultrasound guided percutaneous injection. Patients were then required to follow a specific physical therapy protocol and return for follow-up evaluation 12 weeks post-treatment using the same questionnaires.

A majority of patients reported significant improvement in their symptoms with some reporting complete resolution of pain in certain activities. However, due to the small patient population, these results were not statistically significant. Future research in this area should include a larger population, more objective measures of improvement, and a randomized, controlled study. Although promising, the use of PRP injections in treating high hamstring tendinopathy requires further evidence in order to be a widely accepted form of treatment.
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<tr>
<td>AAOS</td>
<td>American Academy of Orthopaedic Surgeons</td>
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<td>bFGF</td>
<td>basic Fibroblast Growth Factor</td>
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<td>BMP</td>
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<td>IGF</td>
<td>Insulin-like Growth Factor</td>
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<td>PPP</td>
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<td>PRP</td>
<td>Platelet-Rich Plasma</td>
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<td>MRI</td>
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<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<td>PDEGF</td>
<td>Platelet-derived Epidermal Growth Factor</td>
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<td>PDGF</td>
<td>Platelet Derived Growth Factor</td>
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<td>RIT</td>
<td>regenerative injection therapy</td>
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<td>tendon</td>
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<tr>
<td>TGFβ</td>
<td>Transforming Growth Factor beta</td>
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<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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BACKGROUND

Hamstring Anatomy and Histology:

The hamstring muscles consist of the semitendinosus, the semimembranosus, and the biceps femoris, along with their corresponding tendons (Figure 1) (Clanton & Coupe, 1998). All muscles with exception of the short head of the biceps femoris originate at the ischial tuberosity at the bottom of the pelvis. The muscles separate into each individual components approximately 5-10 cm from the tuberosity, the first being the semimembranosus, running along the medial side of the femur. Semimembranosus has multiple insertions at the posteromedial corner of the knee, primarily at the posterior tubercle of the medial femoral condyle (Clanton & Coupe, 1998; Sutton, 1984). Both the semitendinosus and the long head of the biceps femoris originate at the inferomedial aspect of the ischial tuberosity (Clanton & Coupe, 1998; Sutton, 1984). The second point of origin for the semitendinosus is an aponeurosis of the semitendinosus and long head of the biceps femoris distal to the ischial tuberosity. The tendon then runs over the tibial collateral ligament, forming part of the pes anserine and inserts behind the attachment of the sartorius below the gracilis onto the proximal medial surface of the tibia. The short head of the biceps
femoris has three origins: the lateral tip of the linea aspera, the lateral supracondylar line, and the lateral intermuscular septum. Eventually, the long and short head muscle fibers combine to form a tendon that inserts at the fibular head and the lateral tibial condyle (Clanton & Coupe, 1998; Sutton, 1984) (Figure 2).

Figure 1: Illustration of Basic Hamstring Anatomy. Figure downloaded from AAOS (http://orthoinfo.aaos.org/topic.cfm?topic=a00408#Anatomy.)
Figure 2: MRI of Normal Hamstring Muscles and Ischial Tuberosity
Three different MRI viewings of the hip (Coronal T1W (A), axial STIR (B), and sagittal T1W (C)) illustrating the normal ischial tuberosity along with the attachments at the origin of the long head of the biceps femoris, the semitendinosus, and the semimembranosus. Figure taken from Beltran et al., 2012
The histology of the muscles shows a possible explanation for its predisposition to overuse injury (Garrett, Califf, & Bassett, 1984). The hamstrings have more type 2 muscle fibers relative to other muscles in the lower extremity, suggesting their potential for high intrinsic tension forces. Combined with the fact that running increases the time the muscles are at maximal stretch, the hamstrings are at an increased risk for injuries (Garrett et al., 1984).

**High Hamstring Tendinopathy:**

High hamstring tendinopathy is an uncommon overuse injury mostly seen in middle to long distance runners (Fredericson et al., 2005). It has been described in the literature since 1988, although it was originally termed “hamstring syndrome” (Puranen & Orava, 1988). However, its presence has been receiving more attention as an important cause for chronic pain in the lower extremities and researchers have altered the nomenclature due to ambiguity of diagnosis in the previous terms (Lempainen et al., 2009; Puranen & Orava, 1988; Zissen et al., 2010).
Diagnosis

Patient history, physical examination, and imaging studies play key parts to the accurate diagnosis of this condition. The clinical triad for tendinopathy includes pain, swelling, and a reduced load bearing capacity (De Vos et al., 2010). Patients with high hamstring tendinopathy typically report deep buttock pain brought on by running, and in more severe cases the pain can be present during prolonged sitting (Puranen & Orava, 1988). Physical examination for high hamstring tendinopathy is generally notable for local tenderness to palpation, pain with stretching, and reduced muscle activation. The tuberosity and the proximal hamstrings are palpated for signs of tenderness or thickening of the area (Fredericson et al., 2005). Tightness is assessed using the bent-knee stretch test (Figure 3), and the supine plank test is used to assess strength of the proximal hamstring (Figure 4) (Fredericson et al., 2005).
Figure 3: Dr. Michael Fredericson performing bent knee stretch test. Figure taken from Fredericson et al., 2005

Figure 4: The supine plank test is used to assess strength of the hamstrings. Figure taken from Fredericson et al., 2005
Positive results on the three tests (tenderness to palpation, positive bent knee stretch and supine plank) are suggestive of an active high hamstring injury (Fredericson et al., 2005).

Radiographic studies play an important part in the diagnosis. Plain film radiographs may demonstrate ischial tuberosity cortical irregularity, ectopic calcifications, bony avulsions, or evidence of sacroiliitis, but are often of limited use unless an avulsion fracture or extensive strain with obvious clinical swelling is present (Clanton & Coupe, 1998). MRI (magnetic resonance imaging) is much more useful for the diagnosis of high hamstring tendinopathy as it can grade the extent of the injury and explore other potential causes for the patient’s symptoms (Zissen et al., 2010). The presence of increased signal on T1-weighted images without significant abnormality on fat-suppressed T2-weighted images is diagnostic for high hamstring tendinopathy (Fredericson et al., 2005) (Figure 5). There may also be stress reaction or bone edema within the ischial tuberosity, or the abnormal tendon findings such as focal partial tears (Fredericson et al., 2005) (Figure 6).
Figure 5: Patient with proximal hamstring tendinopathy.
An MRI (A) and Ultrasound image (B) showings findings consistent with tendinopathy. Using Axial T2-weighting and fat-suppression the image reveals increased T2 signal at the origin of the tendon (arrowhead), characteristic of tendinopathy. In B, hypoechogenicity and heterogeneity (arrows) of the hamstring tendon can be seen (t) at the ischial tuberosity (it). Figure taken from Zissen et al., 2010
In addition to radiographs and MRI, high resolution ultrasound imaging is gaining acceptance because of lower cost, increased patient comfort, and the ability to examine the tissue in real-time. Ultrasound provides superior soft tissue resolution and characterization, particularly for highly organized tissues such as tendons and ligaments. Normal tendons and ligaments appear hyperechoic with linear fibrillar pattern under ultrasound on longitudinal images, whereas tendinopathic tendons appear hypoechoic due to the loss of organized collagen fiber. The tendon may also appear thickened due to the
presence of edema from ongoing inflammatory processes (Fullerton, 2008). With the increased use of ultrasound and MRI on patients with hamstring injuries, physicians are more able to diagnose the source of the pain and to focus treatments specifically to the injured muscle (Zissen et al., 2010). Both MRI and ultrasound can aid viewing of the effects of PRP on the targeted tissue and could be used in other research studies to record changes in tissue morphology and structure after PRP therapy (Lee et al., 2011).

**Treatment**

Conservative management for pain control is typically initiated with physical therapy modalities such as ice, electrical muscle stimulation, and pulsed ultrasound. Unlike acute injuries, non-steroidal anti-inflammatory drugs (NSAID’s) are ineffective in treating chronic tendinopathies (Brukner & Khan, 2011). Correction of biomechanical factors such as pelvic alignment and soft tissue mobilization are also helpful, and the patient is encouraged to begin a progressive strengthening program as soon as possible. Hamstring strength training, especially eccentric exercises, is currently the best-supported treatment for hamstring muscle injuries. Eccentric strengthening helps to prevent tendency of developing shorter, inflexible muscles after injury, and can prepare the
rehabilitating muscle for the greater forces involved in sports (Sherry & Best, 2004). Exercises progress from bilateral non-weight bearing to unilateral closed chain isometrics and isotonic open-chain exercises when bilateral exercises can be completed with no pain (Fredericson et al., 2005). Typically, conservatively managed hamstring injuries are fully resolved in 2-6 months, but in about 20% of patients, symptoms may persist for more than 6 months and require more aggressive treatment methods (Zissen et al., 2010), in which cases, injections of corticosteroids, extracorporeal shockwave therapy, and surgery may be recommended.

**Corticosteroid Injections**

A corticosteroid injection is recommended when other pain management techniques have been unsuccessful, especially in cases of edema surrounding the ischial tuberosity combined with a relatively normal looking tendon. However, steroid injections are not a long-term solution to chronic tendinopathies and is generally prescribed in conjunction with physical therapy regiments to augment the treatment (Fredericson et al., 2005).

**Extracorporeal shock-wave therapy (ESWT)**

Extracorporeal shock-wave therapy is a therapeutic technique originally used in nephrolithiasis treatments, but has become a successful treatment for other
chronic issues such as plantar fasciitis, patellar tendinopathy, and calcific tendinitis of the shoulder (Wang, 2012). The mechanism behind the ESWT is not completely understood but it is thought that shockwaves can cause interstitial and extracellular effects, leading to improved tissue regeneration (Wang, 2012). Randomized controlled studies have shown its effectiveness in treating chronic tendinopathies (Al-Abbad & Simon, 2013; Galasso, Amelio, Riccelli, & Gasparini, 2012) including one study suggesting that ESWT was more effective than conservative management in treating chronic proximal hamstring tendinopathy (Standaert, 2012).

**Surgery**

Surgery should be considered when conservative managements have failed to relieve symptoms of hamstring tendinopathy. Indications include recalcitrant, significant symptoms leading to functional and athletic limitations, and clinical and MRI findings consistent with proximal hamstring tendinopathy (Lempainen et al., 2009). The principle of one surgical procedure published for this condition involves partial tenotomy of the diseased semimembranosus tendon to reduce its thickness (Figure 7). The sciatic nerve is also examined and any adhesions present are released (Lempainen et al., 2009).
Figure 7: Illustration of Surgical Procedure for Proximal Hamstring Tendinopathy: (A) The biceps femoris muscle is moved aside to expose semimembranosus tendon. (B) Partial tenotomy is performed on the tendinous portion of the semimembranous muscle. Additionally, the sciatic nerve is investigated to expose potential adhesions (C) The head of the semimembranosus tendon is attached to the biceps femoris tendon to prevent excess retraction. Figure taken from Lempainen et al., 2009

Wound Healing:

The wound healing cascade is an intricate and complex process. Three phases have been described: (1) the inflammatory phase, (2) the proliferative phase, and (3) the maturation and/or remodeling phase (Lee et al., 2011; Nguyen et al., 2011) (Figure 8). The initial phase, the inflammatory phase, occurs in the first week after injury and involves hemostasis and recruitment of inflammatory mediators. An important part of the inflammatory process involves macrophages and fibroblasts, which are attracted in part by specific growth factors. The production
of these growth factors is stimulated in the process of repair and remains active during the healing stages (Nguyen et al., 2011).

Figure 8: Wound healing cascade. Figure demonstrates the healing cascade including the inflammation, proliferation, and remodeling phases. Figure taken from Nguyen et al., 2011
**Regenerative Injection Therapy:**

In recent years, the injection of endogenous substances to treat acute and chronic injuries has become a topic of great interest and research. The aim of this treatment is to inject growth factors or other substances with regenerative properties into the injury site in order to stimulate a more vigorous healing response and to promote growth and repair of normal cells and tissue. The term “prolotherapy”, which was coined by Hackett in 1950, was originally the general term to describe this type of treatments, but now it is known as regenerative injection therapy (RIT) (Fullerton & Reeves, 2010; Topol & Reeves, 2008). Many different substances have been used including: dextrose, osmotic fluids, irritants, particulates, or chemotactic agents, as well as concentrated autologous blood and platelet rich plasma (PRP). It is thought that healing is achieved through the formation of new collagen fibers through the induction of inflammation after injection (Banks, 1991). In addition to the injected substances, the act of needling which is also known as either tenotomy or fenestration, has also been shown to be an active process in healing (Yelland et al., 2004), although its exact role in tissue healing is still a subject of intense research.
Platelet-Rich Plasma:

Concentrated platelet therapy, or Platelet-Rich Plasma has been in use for around 20 years, but it was not until the New York Times reported PRP playing a deciding factor in the return to play of Pittsburgh Steeler player Hines Ward just in time for the 2009 Super bowl, did the treatment start to gain more widespread popular interest and attention (Lee et al., 2011; Schwarz, 2009). Although some studies have shown the potential efficacy of PRP injections in treating acute and chronic musculoskeletal injuries, such as rotator cuff surgery, elbow tendinosis, patellar tendinosis, and Achilles tendon injuries there remain many questions as to the mode of action, preparation, timing, and other factors involved in its clinical use (Taylor et al., 2011).

Proposed Mechanism of Action

The main rationale behind the use of platelet enriched plasma is two-fold: 1) Platelets are an essential part of the healing cascade and 2) Plasma contains a number of growth factors believed to be involved in healing and the inflammatory response.
Platelets are non-nucleated bodies in the blood that are essential to hemostasis. They contain three types of granules one of which is the alpha-granules. Alpha granules contain a variety of proteins, cytokines, and other bioactive products, which are responsible for stimulating and regulating the process of wound healing (Table 1). The release of certain growth factors from these alpha-granules aids the process of tissue regeneration (Foster et al., 2009).
TABLE 1: Growth Factors Identified Within Platelet-Rich Plasma and Their Physiologic Effect

PD-EGF, platelet-derived epidermal growth factor; PDGF, platelet-derived growth factor; BMP, bone morphogenetic protein; TGF, transforming growth factor; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; ECGF, endothelial cell growth factor; bFGF, basic fibroblast growth factor. Table adapted from Foster et al., 2009.

<table>
<thead>
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<th>Factor</th>
<th>Target Cell/Tissue</th>
<th>Function</th>
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<tr>
<td>PD-EGF</td>
<td>Blood vessel cells, outer skin cells, Fibroblasts, and many other cell types</td>
<td>Cell growth, recruitment, Differentiation, skin closure, Cytokine secretion</td>
</tr>
<tr>
<td>PDGF A + B</td>
<td>Fibroblasts, smooth muscle cells, chondrocytes, osteoblasts, mesenchymal stem cells</td>
<td>Potent cell growth, recruitment, Blood vessel growth, granulation, Growth factor secretion; matrix formation with BMPs (collagen and bone)</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Blood vessel tissue, outer skin cells, Fibroblasts, monocytes, TGF gene family includes the BMPs, Osteoblasts—highest levels of TGF-βr</td>
<td>Blood vessel (±), collagen synthesis, Growth inhibition, apoptosis (cell death), Differentiation, activation</td>
</tr>
<tr>
<td>IGF-I, II</td>
<td>Bone, blood vessel, skin, other tissues, Fibroblasts</td>
<td>Cell growth, differentiation, recruitment, Collagen synthesis with PDGF</td>
</tr>
<tr>
<td>VEGF, ECGF</td>
<td>Blood vessel cells</td>
<td>Cell growth, migration, new blood vessel growth, Anti-apoptosis (anti–cell death)</td>
</tr>
<tr>
<td>bFGF</td>
<td>Blood vessels, smooth muscle, skin, Fibroblasts, other cell types</td>
<td>Cell growth, Cell migration, blood vessel growth</td>
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It is theorized that the presence of increased a-granule may lead to inhibition of excess inflammation along with stimulation of stem cell proliferation and maturation (Paoloni, De Vos, Hamilton, Murrell, & Orchard, 2011). The platelet concentrate seems to modify the natural healing pathway by providing increased concentrations of growth factors and bioactive proteins which in turn stimulates regeneration of tissue with low baseline healing potential, resembling the initial stage of inflammation, and the attraction of leukocytes to the site of injury (Taylor et al., 2011). In vivo and animal studies have shown PRP addition resulted in cell proliferation, collagen deposition, improved gene expression, accelerated remodeling and angiogenic processes, increased anti-inflammatory response, increased fibrillogenesis, and improved collagen matrix (De Vos et al., 2010). PRP also contains fibrin, fibronectin, and vitronectin, proteins important for cell adhesion, osteoconduction and as a matrix for bone, connective tissue, and epithelial migration (Marx, 2004). In addition to the PRP adjuvant, studies suggest that the act of injection is akin to tenotomy, which itself may have a component in the healing process due to induced local inflammation and local bleeding (Yelland et al., 2004).
Preparation and Administration

At the present, there exists little consistency in regards to the preparation and administration of PRP. Taylor and colleagues (Taylor et al., 2011) noted the lack of standardized protocol in their review of PRP injections for tendon and ligament injuries. Researchers and clinicians report varied concentrations of PRP, timing of injection relative to preparation, activation of platelets, and other factors. The majority of preparations were in the form of an aqueous solution, but may include solid substance such as fibrin membranes, fibrin matrices, PRP gels, and the combinations thereof. Platelet concentrations range from $6 \times 10^3$ to $6 \times 10^6$ (per microliter plasma) after centrifugation (Taylor et al., 2011), while another study has suggested the effective concentration to be between $300,000$-$1,000,000$ per microliter (Pietrzak & Eppley, 2005). The average baseline concentration is about $200,000$ per microliter of plasma and studies have reported the minimum increase in concentration to be $1,000,000$ platelets per microliter, or about 4-5 times baseline platelet count (Marx, 2004).

The preparation of PRP involves separating the cellular component from the plasma using centrifuges. After the blood is drawn from the patient, the blood is then treated with an anti-coagulant and spun down resulting in a top layer of
plasma, middle layer of platelets and leukocytes, and bottom layer of red blood cells (Figure 9). Two rounds of centrifugation are often performed in order to concentrate the platelets and to separate out unnecessary components of whole blood (i.e. red blood cells, leukocytes) in order to reduce the risk of immune reactions. An additional round of centrifugation is usually performed to separate the Platelet-poor Plasma (PPP) from the PRP (Paoloni et al., 2011).

Figure 9: Preparation of Platelet-Rich Plasma from Autologous Whole Blood. Figure taken from Nguyen et al., 2011
**PRP Costs**

Currently, due to its investigational nature, PRP injections are generally not covered by insurance plans. Depending on the manufacturer, centrifuge used, and the amount of PRP needed, the cost of a PRP kit ranges from $140-$400. Adding costs of facilities, physician costs, and the cost of the injection procedure, totaling around $750-$2000, PRP may lead to significant cost out-of-pocket for most patients. However, although this may seem pricey, some investigators argue that effective PRP treatments are still much more cost-effective than the typical cost of surgery ($10,000-$15,000) (Nguyen et al., 2011).

**Side Effects**

Side effects of PRP are minimal and the most commonly reported include pain at the site of the injection, inflammation, and stiffness. One review by Paoloni et al., 2011 reported side effect rates between 1-10% with average pain and stiffness of 6.1 out of 10 lasting between 1.5 to 2.4 days.
Specific Aims

PRP has shown a great deal of promise regarding its utility in treating a myriad of orthopedic issues, particularly tendon and ligament injuries. Currently, to the best of our knowledge, there exists only one study reporting the effects of injecting PRP into patients with high hamstring tendinopathy (Mautner et al., 2013). Based on previously reported results in treating other chronic tendinopathies, we believe that similar results may be expected in treating the hamstrings with PRP.

We will examine patient reported data on pre- and post- PRP injection surveys regarding pain levels, activities affected, prior treatments, etc., using these answers as evidence of the degree of recovery achieved in each patient. We will then compile the data and compute valuable statistics to describe the effects of the treatments.

This study hopes to show that patients experiencing chronic symptoms of high hamstring tendinopathy, having attempted and failed physical therapy, will
show significant improvement in their pain levels and activity levels post-treatment.

In addition, we hope to learn about any additional correlations between patient history and clinical outcomes that may be relevant to future treatment guidelines and potentially create future research endeavors.
Methods

Population:

Patients were recruited for this study through a musculoskeletal/pain clinic in a community medical center. The primary patient populations seen at this institution includes both elite collegiate level athletes as well as community recreational athletes of various fitness levels. All patients had been referred by their physicians to receive PRP injections for the treatment of their tendinopathy and must meet the predetermined inclusion/exclusion criteria. The inclusion criteria include: at least 18 years of age, failing physical therapy, have positive MRI signs of high hamstring tendinopathy with or without adjacent bone marrow edema, and have at least one of the following positive clinical findings such as tender to palpation at the site of the ischial tuberosity, positive bent knee stretch test, positive supine plank test, positive prone resisted knee flexion or positive prone resisted hip extension. The exclusion criteria for this study include the presence of other acute injuries to the lower limb, concurrent pregnancy, minors, or the presence of malignant disease.
Patients meeting the inclusion criteria without exclusion criteria were approached and recruited. Additional information was gathered for complete baseline evaluation, including a Lower Extremity Functional Scale questionnaire (Binkley, Stratford, Lott, & Riddle, 1999) (Appendix 1). Patients were then scheduled for a PRP injection at either one of the two clinical sites. Patients then received a single percutaneous PRP injection prepared and administered according the study protocol parameters described in the following sections.

**PRP Preparation:**

PRP was prepared using the BioMet System. Antecubital venipuncture was used to draw approximately 60 cmL of the patient's blood, followed by centrifugation for 15 min, yielding approximately 6-8 mL of PRP, which was then transferred to a sterile 12 ml syringe. Sodium bicarbonate (8.4%) was added as a buffer to the PRP at a concentration of 0.05% to match the pH of the tendon tissue, in order to reduce potential patient discomfort.
Ultrasound Procedure:

The patient is placed on the examination in prone position, and the gluteal regions were examined under ultrasound. The proximal hamstring tendon origin was identified by transverse and longitudinal scanning using a high frequency transducer (GE HealthCare Logic 9, UK). Local blood vessels and the sciatic nerve were identified. After identifying the target, a 21 gauge, 1.5 inch needle was guided to the target in a in-plane approach towards the hamstring tendons for injection of local anesthetic with 1% lidocaine. Subsequently, the area was anesthetized with approximately 5 cc of 0.5% bupivacaine.

Tenotomy and PRP Injection:

In thin patients, the hamstring tendons may be reachable with the 21 gauge, 1.5 inch needle used for anesthesia. In larger patients, a longer spinal needle is inserted into the proximal tendons under direct ultrasound guidance. Further anesthetic is then injected at the tendon/bone interface. This procedure is done while the PRP is being prepared in the centrifuge. The PRP is injected slowly under US guidance, targeting areas of focal hypoechoic echotexture or areas of partial tearing. Injection is performed during gentle advance and retraction of the needle, in order to deposit the PRP deep, interstitial, and superficial to the
tendons. Typically, 5 passes of the needle through different areas of the tendons are used for needle tenotomy. In addition to tenotomy, the spinal needle is used to probe the ischial tuberosity itself, with the aim of stimulating the periosteum or releasing marrow factors, though the bone is typically very firm and the marrow space is not entered directly. Post PRP injection, mild pressure is applied to the site to distribute the injected materials further about the hamstring tendons and to minimize any local bleeding. Patients are kept prone for an additional 10 minutes following the procedure.

**Post-Treatment Protocol:**

Following injection, all patients were asked to observe a 1 week rest period with non-weight bearing for first 2 days, then progressive weight bearing using crutches advanced through the remainder of the week. After the first week, patients began physical therapy per protocol (Table 3).

All patients were asked to revisit the clinic for a reevaluation after the 12th week.

Based on the clinical evaluation, a new MRI was recommended if the recovery level was not as expected. At this point, the patient may proceed to continue with a second PRP injection or elect to undergo surgery consultation.
<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Physical Therapy Protocol</th>
</tr>
</thead>
</table>
| **0-2 weeks** | 1) 2 days non-weight bearing lower extremity  
Walking assisted with crutches  
Ice allowed at the injection site  
2) Partial weight-bearing with crutches  
   Progressively increase weight-bearing as tolerated.  
   Ice, compress, elevate. AROM multiple times per day. |
| **2-4 weeks** | Multi-planar isometrics and gentle passive stretching in addition to AROM  
   May begin weight-bearing as tolerated in the lower extremity  
   Continue edema control measures (i.e.: compression, ice, elevation)  
   Stationary bike without resistance and no standing while biking. |
| **4 weeks** | Begin gentle isotonics  
May add resistance to bike but no standing  
May begin elliptical machine. |
| **6 weeks** | Begin eccentric protocol  
May transition to treadmill  
Begin with walking and progress to jogging over next couple of weeks |
| **10 weeks** | Begin plyometrics, sports specific drills. |
| **12 weeks** | Begin plyometrics, sports specific drills. |
Statistical Analysis:

We defined patients with “significant improvement” as those whose LEFS increase by at least 9 points, according to the standards of the authors outlining the assessment (Binkley et al., 1999).
Results

At the time of this paper, 15 PRP injections had been performed. Only 3 patients declined to participate in the study. Of the remaining 12 participants, 3 were excluded due to the lack of the completion of the initial LEFS questionnaire, 1 due to a lack of 12 week follow-up evaluation, and 1 for not meeting the inclusion criterion of having attempted and failed physical therapy. As a result, 7 total patients were included in the analysis. The mean age of included patients was 48.4 years with the majority being female (5/7, or 71.4%). 1 patient reported complete resolution of pain at rest. 2 out of 7, or 62.5%, reported duration of their symptoms as greater than 6 months, and 3 out of 8 (37.5%) reporting symptoms persisting for one year or more. All patients in this study had undergone and failed physical therapy. Many reported additional treatments including NSAID’s (4/7, or 57.1%), corticosteroid injections (7/7 or 100%), and other alternative and complementary treatments such as acupuncture or massage (4/7, or 57.1%). The patient characteristics are summarized in Table 3.

The average LEFS for patients pre-treatment was 47.7, ranging from 11-67. The average maximal function percentage was 59.6%, ranging from 13.8%-83.8%. On
12 weeks post-treatment follow-up, the LEFS average increased to 65.0, ranging from 49-75. Maximal function post-treatment was 81.3%, ranging from 61.3%-100%. This corresponds to an average increase in LEFS and Maximal Function of 17.3 units and 21.6%, respectively. The difference was not statistically significant due to the small sample size. Clinical outcomes are summarized in Table 4.

Table 3: Patient Characteristics and Prior Treatments

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>2(28.6%)</td>
</tr>
<tr>
<td>31-60</td>
<td>3(42.9%)</td>
</tr>
<tr>
<td>&gt;61</td>
<td>2(28.6%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5(71.4%)</td>
</tr>
<tr>
<td>Male</td>
<td>2(28.6%)</td>
</tr>
<tr>
<td><strong>Prior Treatments</strong></td>
<td></td>
</tr>
<tr>
<td>NSAID’s</td>
<td>4(57.1%)</td>
</tr>
<tr>
<td>Physical Therapy</td>
<td>7(100%)</td>
</tr>
<tr>
<td>Steroid Injections</td>
<td>7(100%)</td>
</tr>
<tr>
<td>Other</td>
<td>4(57.1%)</td>
</tr>
</tbody>
</table>
Table 4: Clinical Outcomes for 8 of 15 Patients Receiving PRP Injections

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Symptoms Prior to Injection</td>
<td></td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>6 months to 1 year</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Degree of LEFS improvement</td>
<td></td>
</tr>
<tr>
<td>Significant (Difference &gt;9)</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>Moderate (Difference &gt; 0)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>None (Difference &lt; 0)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Degree of At Rest Pain Resolution</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>0% &lt; x &lt; 50%</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>&lt;0%</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Degree of Maximum Pain Resolution</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>0% &lt; x &lt; 50%</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>&lt;0%</td>
<td>2 (28.6%)</td>
</tr>
</tbody>
</table>
Platelet-rich plasma has recently gained widespread attention (Schwarz, 2009), despite its use for over 20 years. Although there have been a number of studies regarding its use, there is little consensus regarding its indications, preparation method of delivery, and efficacy (Foster et al., 2009; Taylor et al., 2011). At the present, there have been no studies reported on the use of PRP in treating high hamstring tendinopathy. The patients included in this study were recommended to undergo PRP injections by their treating physicians due to their lack of response to eccentric hamstring training with physical therapy and corticosteroid injection. Eccentric strengthening is considered as the gold standard for chronic tendinopathy.

Many of the patients included reported significant improvements in their symptoms and overall athletic capabilities, while a smaller percentage reported no benefit from the treatment or even a lower LEFS. An increase in LEFS greater than 9 is suggestive of significant improvement (Binkley et al., 1999). Although we see an average LEFS difference in 18.9 in this study (much greater than 9), these improvements did not achieve statistical significance (P=0.076) due to the
lack of statistical power secondary to the small sample size. As many as 50% of patients experienced both significant reductions in at rest pain levels as well as significant improvement in LEFS, with multiple patients reporting complete resolution in many activities on the LEFS.

There were multiple limitations that potentially affected the outcomes of our research. First, the small sample size limited the statistical power of the study. Second, questionnaires can lead to subjective results, can be influenced by recall, and it is difficult to compare the results of one patient with another. Objective data regarding the effects of PRP on hamstring tendinopathy can be obtained through imaging studies such as MRI and ultrasound by comparing pre- and post- treatment images, but that would not necessarily correlate to patient symptoms or functional status. Third, the standard follow-up time was set at 12 weeks, but it is possible that the healing timeline is highly variable and the full healing potential of PRP may take significantly longer for some patients. Currently, there are no clear guidelines of duration of treatment effect and follow-up timeline. Including follow-ups for times longer than 12 weeks may better demonstrate the long-term outcome of the PRP treatment. Lastly, given the retrospective study design, neither the patients nor the clinicians were blinded.
There were no controls besides historical control, which cannot rule out the influence of other confounding factors.

**Future Research**

Although not statistically significant, the results of this study do show promise for the use of PRP in treating high hamstring tendinopathy. Future studies with larger patient sample size sufficient to achieve statistical power can help determine the clinical effect seen in this study. Subgroup analysis with sufficient follow up may better delineate the onset and the duration of treatment benefit, the degrees of symptoms and functional improvement, and the demographic or biomechanical factors influencing them. Pre- and post-treatment imaging studies using MRI or ultrasound can help demonstrate the macroscopic tissue changes, which can then be correlated with symptoms and function. Lastly, randomized double-blind controlled study design should be conducted to remove the confounding factors involved.
Appendix 1: Patient Baseline Evaluation Form

Injection date:

Age:

Gender:

Injection side:  Right / Left

Allergies / Medical conditions:

Sports performed (hours per week / mileage):

Mechanism of injury:  Acute  Chronic  Previous injury

Duration of hamstring symptoms:

Prior treatments:

<table>
<thead>
<tr>
<th>AINSD</th>
<th>Physical Therapy</th>
<th>Steroid injections (n°__)</th>
<th>Other</th>
</tr>
</thead>
</table>

Pain score (0-10):  At rest__  Maximal pain__

Activities make pain worst:

Ability to continue sports: *Impact in patient’s sport life*

Pain with sprinting or accelerating. 0 1 2 3 4

Pain running uphill/downhill. 0 1 2 3 4
Appendix 2: Low Extremity Functional Scale

**Instructions**

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention. Please provide an answer for each activity.

Today, _do you or would you_ have any difficulty at all with:

<table>
<thead>
<tr>
<th>Activities</th>
<th>Extreme difficulty or unable to perform activity</th>
<th>Quite a bit of difficulty</th>
<th>Moderate difficulty</th>
<th>A little bit of difficulty</th>
<th>No difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any of your usual work, housework or school activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Your usual hobbies, recreational or sporting activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting into or out of the bath.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Walking between rooms.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Putting on your shoes or socks.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Squatting.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Lifting an object, like a bag of groceries from the floor.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Performing light activities around your home.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Performing heavy activities around your home.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Getting into or out of a car.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Walking 2 blocks.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Walking a mile.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Going up or down 10 stairs (about 1 flight of stairs).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Standing for 1 hour.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Sitting for 1 hour.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Running on even ground.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Running on uneven ground.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Making sharp turns while running fast.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Hopping.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Rolling over in bed.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Column Totals:**

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doi:10.3810/psm.2005.05.89


doi:10.1016/j.apmr.2007.09.017


doi:10.1016/j.pmr.2010.06.003


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EDUCATION

BOSTON UNIVERSITY SCHOOL OF MEDICINE, BOSTON, MA
M.A., Medical Sciences, GPA: 4.0, September 2011-Present
- **Awards:** Joe Nicholson Medical Scholarship- $1500 awarded to former students of the Burney-Fall River school district showing academic excellence while pursuing a career in medicine

UNIVERSITY OF CALIFORNIA, BERKELEY, BERKELEY, CA
B.A., Molecular and Cell Biology, GPA: 3.52, August 2006 - May 2010
- **Awards:** Davenport Family Scholarship- $4000 awarded to two recipients nationally for academic excellence and demonstrated leadership abilities

WORK HISTORY

CLINICAL RESEARCH ASSISTANT, STANFORD UNIVERSITY
Redwood City, CA, August 2010-Present
- Collected vital data from 100 patient histories in order to present a case-series study
- Organized narrative documents into a standard form in order to elucidate significant correlations between history and injury
- Reviewed journal articles to obtain relevant background information as well as ensure originality of the study

PHYSICAL THERAPY AIDE, EMERYVILLE SPORTS PHYSICAL THERAPY
Emeryville, CA, May 2010- February 2011
- Provided support and biomechanical feedback to patients regarding stretches and strengthening exercises
- Rehabilitated patients using modern symptom-reducing modalities such as ultrasound and electronic muscle stimulation
- Catalogued and documented history, treatment guidelines, and insurance information for more than 50 patients

CHIROPRACTIC ASSISTANT, INNERSPORT CHIROPRACTIC
Berkeley, CA, July 2010-August 2010
- Greeted, scheduled and collected from current and new patients
• Provided personal training support to patients in strengthening and stabilization exercises
• Insured efficiency of a fast paced clinic by performing multiple receptionist tasks and errands

SPORTS MEDICINE INTERN, UNIVERSITY OF CALIFORNIA, BERKELEY SPORTS MEDICINE
Berkeley, CA, January 2008 – August 2010
• Assisted athletic trainers, doctors, and physical therapists in clinical and on-field injury diagnosis and treatment
• Catalogued patient history and therapy information for more than 50 intercollegiate athletes
• Rehabilitated injured athletes using modern physical therapy technology and strengthening exercises

MEDICAL AND LEADERSHIP ACTIVITIES

VOLUNTEER/STUDENT INTERN, ISTITUTO LUIGI CONFIGLIACHI
Padova, Italy, September 2009 – December 2009
• Assisted in performing basic hygiene procedures
• Actively observed and participated in the diagnosis and therapy of hospice care patients in Padova

VOLUNTEER, ARICONFRATERNITA DI MISERICORDIA DI SIENA
Siena, Italy, Summer 2009
• Worked with volunteer ambulance team to provide first response emergency medical assistance
• Assisted in transporting elderly, disabled, and chronically ill Italian patients to and from the local hospital

SKILLS

• Italian (Fluent)
• Spanish (Basic)
• Proficient in Microsoft Office applications such as Word, Excel, PowerPoint, and E-mail
• Knowledge of Genbook online scheduling application
• Proficient in cell biology laboratory techniques, including PCR, ICC, SDS-PAGE, Western Blot, and molecular cloning