STUDY PROTOCOL

Official Title: Ultrasound-guided platelet-rich plasma versus whole blood injection for the treatment of gluteus medius tendinopathy: a double-blind randomized controlled study

NCT02978833

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Specific Aims or Research Questions

1.0 What is the condition or intervention to be studied?

We are studying the use of platelet-rich plasma (PRP) injections for the treatment of gluteus medius tendinopathy, which is often referred to as Greater Trochanteric Pain Syndrome (GTPS). This condition is characterized by pain in the lateral aspect of the hip that is aggravated by side lying, stair climbing, and walking. The underlying pathophysiology is tendinosis or partial thickness tear of the abductor muscles of the hip (most commonly the gluteus medius). This condition is identified by history, physical exam, and confirmatory MRI or ultrasound of the hip.

2.0 What is/are the research question(s)/specific aim(s)? Pose very specific questions that can be addressed within the proposed design of the study. Prioritize them in order of importance.

Does injecting autologous platelet-rich plasma into a gluteus medius tendon with tendinopathy and partial tear result in greater improvement in pain and function than does injecting whole blood alone?

3.0 What is/are the hypothesis(es)?

An injection of platelet-rich plasma into the affected gluteus medius tendon will improve pain and function related to this condition with greater efficacy than does injecting whole blood alone.

4.0 Identify and <u>define</u> the primary outcome and when the outcome will be measured. If measuring change in post-operative function is the most important, that will be your primary outcome.

The primary outcomes are improvement in pain, function, and patient satisfaction following platelet-rich plasma or whole blood injection. These outcome measures will be measured via the Numerical Rating Scale for Pain, Non-Arthritic Hip Score, Veterans RAND 12-Item Health Survey, and a 10-cm visual analog scale (VAS) for patient satisfaction which will range from ‘‘very dissatisfied’’ to ‘‘extremely satisfied.’’

The primary outcome measures will be recorded on day of injection, then 6 weeks, 3 months, 6 months, 9 months, and 1 year post-injection

5.0 Identify and <u>define</u> the secondary outcome(s) and when they will be measured (list additional goals one at a time with their corresponding outcomes).

Secondary outcomes include the Forward Step-down Test (FSD) and patient reported pain during resisted side-lying hip abduction. Patient reported pain during the FSD and resisted side-lying abduction will be measured using a 10-cm visual analog scale (VAS). Other secondary outcomes include any untoward side-effects including increased pain, bleeding, and

infection.

The FSD and resisted side-lying hip abduction outcome measures will be recorded on day of injection, then 3 months, 6 months, and 1 year post-injection.

All other secondary outcome measures will be recorded on day of injection, then 6 weeks, 3 months, 6 months, 9 months, and 1 year post-injection

BACKGROUND - Be sure to answer each question individually

1.0 Explain why these research questions are being asked:

There is no current prospective literature regarding PRP or whole blood injections for the treatment of gluteus medius tendinopathy despite having evidence that these treatments may positively affect tendon healing. It is unknown whether injection with PRP for tendinopathy is more efficacious than injection with whole blood alone. This study may demonstrate efficacy of PRP injections for the treatment of gluteus medius tendinopathy, which would offer patients a potential treatment option prior to the consideration of surgery.

2.0 What is the background of the topic that you believe is important for the reviewer to know in considering this protocol, including prior studies by this research team. Describe strengths and deficiencies of prior studies; explain how this study fits in. Include references.

Greater Trochanteric Pain Syndrome (GTPS) caused by a constellation of issues but most commonly tears of the gluteus medius or minimus at the tendon or musculotendon junction, though prevalent, can be misdiagnosed and unrecognized by clinicians evaluating patients who present with lateral hip and occasionally, thigh pain. In a study conducted by Howell et al., 20% of 176 patients undergoing a total hip arthroscopy were found to have a gluteus medius or minimus tear that was missed upon clinical exam prior to surgery.[18] Tears can be misdiagnosed because pain often presents in the pattern of greater trochanteric pain syndrome (GTPS), tenderness to palpation over the greater trochanter when the patient is in a side-lying position, and is attributed to trochanteric bursitis, a diagnosis that can be disputed with better imaging and attention to anatomy.[4,6,8,10,12,13,25-28,33]. Due to the high prevalence of GTPS, estimated to be in 10%-25% of the population, the limited literature and treatment options of gluteus medius tears is surprising [33,38]. This is an area that needs more research attention to help our understanding of the condition and develop other less invasive treatments. In addition, the pain and disability associated with hip abductor tendons that go on to complete tears can be significant. An early treatment that promotes healing may limit the future morbidity associated with end stage hip abductor loss.

The current treatment of GTPS due to gluteus medius tendinopathy is limited to lifestyle modifications to help with the anti-inflammatory response, corticosteroid injections, physical therapy, and open and endoscopic surgical repair [13,16,36,38]. If pain does not resolve with oral medications and physical therapy, surgical intervention although not commonly performed is

considered. Surgery typically involves open vs. endoscopic transfer debridement and/or transfer of the gluteus maximus tendon to improve hip abduction strength. This type of surgery has a prolonged recovery with only modest outcomes. Studies involving small numbers of patients report rest from sport for four months post-procedure at which point sport-specific training can resume[36]. For the high-functioning individual and athlete eager to return to sport this is a less than ideal option; however, ignoring or not recognizing partial-tears can result in a more debilitating full-thickness tear.

A potential alternative to surgery could be the use of PRP or whole blood to treat GTPS. This would be a cost-effective option with a shortened recovery time, allowing individuals to return to sport and daily functioning sooner.

The rationale behind proposing PRP as a treatment option comes from the age old comparison of the muscles of the hip to the rotator cuff of the shoulder[7,14,22]. This analogous model allows us to predict that successful treatments, such as platelet rich plasma injections, in treating rotator cuff tears could show similar success when treating gluteus medius tears. Generally, the tendon heals at a slower rate when compared to other connective tissues. One reason that explains this phenomenon is the poor vascularity of tendons [15,17,24] and it has been hypothesized that improving angiogenesis and aiding in tissue remodeling via the release of VEGF within the PRP, healing can be improved. The theory supporting the use of PRP in treating these various musculoskeletal conditions is based on the concept of reparative healing. In this context, growth factors are considered essential in the healing process and tissue formation.[37] PRP is considered rich in these growth factors that are contained within the platelet alpha granules. Platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), and insulin-like growth factor (ILGF) are a few of the growth factors contained within alpha granules which are proven to be powerful agents in stimulating duplication, activation, and growth of mesenchymal cells (mainly osteoblasts, fibroblasts, and endothelial cells) and, finally, tissue regeneration.[34] Furthermore, these growth factors also promote proliferation, cell migration, and synthesis of extracellular matrix proteins [1,3,23,31].

The literature regarding the use of and efficacy PRP in rotator cuff repair is limited with mixed results. In a study conducted by Barber et al.[2] 40 patients underwent arthroscopic repair of a torn rotator cuff. Twenty patients received PRP and twenty patients acted as the control. After a minimum of 24 months, all patients received an MRI scan in order to evaluate the healing progress of the rotator cuff. It was found that the PRP group had lower rates of re-tearing in comparison to the controls, indicating better recovery. However, the only clinical difference between groups was in the Rowe scores for instability.[2] Another arthroscopic rotator cuff study argues that patients who received PRP showed reduced pain in the earlier months in comparison to controls.[30] While there are promising results indicating that PRP may facilitate recovery, a third study shows results on the contrary. This prospective cohort study conducted by Jo et al.[21] followed 42 patients who presented with full-thickness rotator cuff repair. Nineteen patients received PRP during surgery, but the results indicated that there was no significant difference in post-operative recovery time, re-tear rate, pain, strength, and range of motion.[21] The presented data shows the promising, but also inconclusive results from PRP

usage in rotator cuff repair.

Our center has completed a retrospective study evaluating PRP for gluteus medius tendinopathy. Of the 10 patients who met the criteria for this retrospective case series, 9 were female and 1 was male. The average age of the patients was 64.7 years. Mean follow up with 10.2 months (range 6 to 26 months). The average pain score as measured by Visual Analog Scale (VAS) was 8.10 (SD 1.7) pre-injection and 3.8 (SD 2.7) post-injection ($p = 0.002$). Overall patient satisfaction was 80% as measured by North American Spine Society Satisfaction Scale (NASS). Two patients reported no improvement. Of the 8 patients who reported improvement, their mean Functional Rating Index (FRI) score was 62.4 (out of 100) before their PRP injection and 21.3 six months post-injection ($p = 0.001$). The average pain score (VAS) among these 8 patients was 8.7 (SD 1.1) pre-injection and 2.7 (SD 2.1) post-injection.

A prospective study evaluating the efficacy of autologous whole blood injection to treat tendinopathy of lateral epicondylitis demonstrated significantly positive results with regard to pain, satisfaction, and ultrasound morphology of the affected tendon.[11] While PRP is more commonly used for injection therapy in tendinopathy, the extent to which PRP is more efficacious than whole blood remains unclear due to lack of high quality prospective studies comparing these two treatments.

Extrapolating from current research, this study seeks to advance PRP research with a double-blind randomized trial comparing autologous PRP versus whole blood injection to treat GTPS due to gluteus medius tendinopathy. It will also provide evidence to guide management for GTPS in cases refractory to more conservative treatment options.

Study Design

Experimental:

Name	Description
Randomized Controlled Clinical Trial	This is the "gold standard" for clinical research. These prospective studies have at least two groups. Patients meeting strict inclusion/exclusion criteria are enrolled and randomly assigned to receive either an experimental intervention or to receive what is considered to be an acceptable alternative – usually the current standard of care or a placebo (e.g., study of hylauronic acid injection versus cortisone for arthritis).

Recruitment

1.0 Check all that apply to describe your study population:

Population
Patients

2.0 Inclusion Criteria:

- Moderate to severe lateral hip pain for greater than 3 months
- Symptoms are refractory to conservative treatment, including at least 8 weeks of traditional physical therapy for this condition
- Moderate to severe gluteus medius tendinosis with or without partial tear <1cm
- Normal neurologic exam except for hip abductor weakness on the affected side.

3.0 Exclusion Criteria:

- Severe (Tonnis grade >1) hip osteoarthritis with active synovitis or bone edema
- Active lumbar radiculopathy with pain, numbness or weakness in a dermatomal distribution.
- No evidence of fatty atrophy, denervation, or complete tears of gluteus medius seen on MRI.
- Any condition that requires anti-platelet or anti-coagulation therapy, including aspirin therapy for cardiac conditions
- Non-English Speaking

4.0 Age Range:
30-65 years

Target Enrollment

1.0 * What is the maximum number of subject you plan to enroll in this study at HSS?(Please enter a number)
72

Interventions and Observations

1.0 Be specific and describe the Interventions or Observations that will be part of this research project. Include a detailed description of the treatment arms, if applicable.

General information related to the patient, including age, sex, duration of symptoms, etc., will be obtained from patient charts. Numerical Rating Scale for Pain, Non-Arthritic Hip Score, and Visual Analog Scale (VAS) for patient satisfaction will be collected. The VAS will also be used to measure the patient's pain during resisted side-lying abduction and during a Forward Step Down (FSD) test. The quality of the movement during the FSD test will also be assessed.

For the Forward Step-down Test (FSD), the patient will stand on a 22-cm step. Patients will then be asked to step down with their asymptomatic limb by bending only the knee on their

symptomatic side until the heel of the asymptomatic side touches the floor, without weight bearing on the heel. Once their heels reach the floor, they will be asked to immediately re-extend the knee on the symptomatic limb to return to the starting position. While performing this movement, the patients will be asked to keep their trunk straight with their hands on their waist. Once they are familiar with the movements, they will be asked to perform 5 consecutive FSD movements.

After the 5 consecutive trials of the FSD test, the examiner will assess the quality of the movement as either good movement quality, moderate movement quality, or poor movement quality based on the following 5 criteria:

1. Arm strategy: if the patient uses an arm strategy to recover balance, 1 point will be given. Because subjects will be instructed to keep their hands on their waist, removing their hands from their waist will be interpreted as a strategy to recover balance.

2. Trunk movement: if the patient leans the trunk to either side, this will be interpreted as recovering balance, 1 point will be given.

3. Pelvic plane: if 1 side of the pelvis is rotated in the transverse plane or elevated in the frontal plane compared with the other side, 1 point will be given.

4. Knee position: if the knee of the tested limb moves medially in the frontal plane and the tibial tuberosity crossed an imaginary vertical line positioned directly over the second toe of the tested foot, 1 point will be given. If the knee moves medially and the tibial tuberosity crosses an imaginary vertical line positioned directly over the medial border of the tested foot, 2 points will be given.

5. Maintenance of a steady unilateral stance: if the patient had to support body weight on the non-tested limb, or the foot of the tested limb moves during testing, 1 point will be given.

A total score of 0 or 1 will be classified as good movement quality, a total score of 2 or 3 will be classified as moderate movement quality, and a total score of 4 or more will be classified as poor movement quality.[39]

The FSD movements will be recorded neck-down and stored on Citrix ShareFile for future evaluation by a single, blinded investigator.

The patient's pain while performing the FSD will be collected using a Visual Analog Scale.

The patient's pain while performing resisted, side lying hip abduction will also be collected. The patient will be asked to lie on the asymptomatic side, with the hip in approximately 30° of abduction and 5° of extension with their toes pointed downward. One hand of the examiner will be placed on the iliac crest and the other hand will be placed on the lateral portion of the knee. The patient will then be asked to maximally abduct the hip against manual resistance.

Their pain will be recorded following this test using the Visual Analog Scale.

The Forward Step-down Test will be performed pre-injection as well as 3 months, 6 months, and 1 year post-injection. All remaining data will be collected pre-injection and following injection 6 weeks, 3 months, 6 months, 9 months, and 1 year. Questionnaires will be completed either on paper at the time of a normally scheduled office visit, mailed to the study subject in a pre-paid envelope, or online.

Patients who meet all inclusion and exclusion criteria will undergo randomization to either the PRP group or the whole blood group. Participants in both groups will have 60 ml of their blood processed via a Arteriocyte Medical Systems centrifuge according to the instructions in order to produce 4 mL of platelet-rich plasma, of that 3 mL will be injected in participants' gluteus medius tendon. The remaining 1 mL aliquot will be brought to the Hematology Lab for CBC with full differentials. The process of collecting and processing the patient's blood into platelet rich plasma will be performed under sterile precautions and will be maintained within sterile containers at all times to decrease the potential risk for infection.

The injections will be performed under ultrasound guidance. 2 cc of 1% lidocaine will be administered locally in order to anesthetize the region prior to injections in both groups. Lidocaine will not be added to the PRP/whole blood or injected into the gluteus medius tendon.

Each PRP and whole blood injection will consist of 3 mL of either autologous platelet-rich plasma or whole blood, respectively. A 22 gauge needle will be used to inject the PRP or whole blood under ultrasound guidance, in the longitudinal plane, into the hypoechoic and tender regions overlying the greater trochanter. A needle tenotomy technique will be used that we define as 6-9 passes of the needle through the hypoechoic region of the gluteus medius tendon.

The tasks involving blood collection, preparation of platelet-rich plasma, whole blood, and of the injectable syringe will be performed by one of the Physiatry research fellows. The study injection with either PRP or whole blood will be performed by one of the attending study investigators who will be blinded to the patient's treatment allocation. There are no visible features that would distinguish the PRP from whole blood within the prepared syringe.

Following the procedure, patients will be instructed on relative rest for 24 hours, and to refrain from the use of NSAIDs for 4 weeks. Acetaminophen may be used for pain control.

All patients will be required to participate in a structured home exercise program beginning 2 weeks post-injection. In order to ensure standardization for this, all patients will receive two individualized physical therapy sessions with a physical therapist for instruction on these exercises, which will focus primarily on strengthening the hip abductors. Patients will also receive a handout with specific exercise instructions as a guide for their home exercise program. They will also be asked to complete an exercise log in order to help assess

compliance with their home exercise program.

Follow-up study questionnaires on pain, function, and satisfaction will be administered as previously stated.

At 6 months post-injection, the participants who do not report satisfactory improvement will be unblinded, and those who were in the whole blood group will be offered an opportunity to receive a PRP injection for their gluteus medius tendinopathy.