Platelet-Rich Plasma for Grade II and III Medial Collateral Ligament Tears in Patients Aged 18-45

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PLATELET-RICH PLASMA FOR GRADE II AND III MEDIAL COLLATERAL LIGAMENT TEARS IN PATIENTS AGED 18-45

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

May 2020

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ABSTRACT:

Medial collateral ligament tears are the most common knee ligament injury. Extent of injury is graded on a three-point scale. The mainstay of treatment for isolated tears is physical therapy; however, grade II and III tears require more intensive therapy. Platelet-rich plasma therapy is an autologous concentration of platelets prepared as an injection to augment the healing process. We propose a randomized controlled trial investigating the efficacy of platelet-rich plasma injection for patients with acute grade II or III medial collateral ligament tears. Results will be quantified by mean decrease in Visual Analog Scale scores at two, four, and six weeks. We hypothesize that injection of platelet-rich plasma combined with physical therapy will significantly decrease pain scores when compared to standard physical therapy. This study will evaluate a new treatment for acute isolated grade II and III medial collateral ligament tears in decreasing pain and expediting return to activity.
CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

1.1.1 Brief History of the Problem

The medial collateral ligament (MCL) of the knee is the most commonly injured ligament at various athletic levels and ages\(^1\)-\(^6\). The MCL is the primary resistor to valgus stress and therefore the mechanism of injury is typically due to contact to the lateral aspect of the knee causing excessive valgus stress\(^4,7\)-\(^10\). The resulting injury can be stratified by clinical grades, I, II, and III\(^4,6\). The treatment of MCL sprains, especially less severe grade of injury, grades I and II, is mainly conservative with emphasis on functional rehabilitation\(^2,3,7,11,12\). The rationale is that compared with the other knee ligaments, the MCL has the most potential to heal after acute injury\(^5,13\). The definition of an acute MCL injury is a date of injury less than three weeks before starting treatment\(^14\). As the severity of the MCL injury increases, there is no consensus on optimal treatment. With more severe grade II and isolated grade III injuries, conservative versus surgical treatment is considered. However, studies have shown that surgical intervention has not yielded a significant clinical benefit after two years, and has even been implicated in poorer outcomes in some studies\(^15,16\). Therefore, conservative treatment is often chosen for isolated grade II and III tears with the resulting time lost due to injury ranging from three to eight weeks\(^7,9,17,18\). This loss of time due to injury indicates the need for augmentation of current functional rehabilitation for isolated grade II and III MCL tears.

1.1.2 Epidemiology and Etiology of Medial Collateral Ligament (MCL) Tears

MCL injury is a particularly common injury in athletes and accounts for up to 7.9\% of all knee injuries\(^8,19\). MCL injury is the most common knee injury in high school,
collegiate, and professional football\textsuperscript{7,17}. Annually, 24.2 per 100,000 high school football players tear their MCL\textsuperscript{3,7,17,18}. A study examining the distribution of MCL injuries among the United States Military Academy and found an overall incidence rate of 7.27 per 1000 person-years\textsuperscript{1}. Men were 2.6 times more likely to sustain an MCL tear than women\textsuperscript{1-3}. Other studies report that injury to the MCL accounted for 29\% of all knee injuries in Division I Football in the United States\textsuperscript{9}. Similarly, MCL injury is the most common knee ligament injury in professional soccer\textsuperscript{20}. Players were 9 times more likely to be injured in a game setting versus during practice and injury was often due to contact with another player or object\textsuperscript{20}. This differs from another common injury, the anterior cruciate ligament (ACL) in which injury due to contact was only the case for 37\% of patients\textsuperscript{21}.

1.1.3 Medial Collateral Ligament Pathophysiology

The medial collateral ligament consists of a superficial and a deep layer\textsuperscript{2,7}. The superficial MCL is the main constraint to valgus stress and is the largest structure of the medial knee\textsuperscript{3,6,7,10,22}. The classic model of healing involving hemorrhage, inflammation, cellular proliferation, and tissue remodeling, and the abundant vascular supply of the superficial MCL allows this process to occur\textsuperscript{3,23,24}. The deep MCL is thicker than the superficial MCL and runs parallel to it until it meets the joint capsule of the knee\textsuperscript{7,21}. The superficial MCL is more commonly injured than the deep MCL, and MRI imaging is a common way to confirm the grade of the sprain\textsuperscript{21}. Grade III tears are commonly associated with injury to the deep MCL but initially might not be clinically appreciated which can later cause residual pain or failure of conservative treatment\textsuperscript{5,21}.

1.1.4 Diagnosis of Medial Collateral Ligament Tears
Diagnosis of MCL injury begins with physical exam with the most common findings being ecchymosis and painful swelling over the medial joint line\textsuperscript{6,14,17} accompanied by tenderness over the medial epicondyle, joint line, or the proximal tibia\textsuperscript{10}. The American Medical Association classifies MCL tears into grades I, II, III\textsuperscript{3}. Grade I includes localized tenderness without evidence of instability, grade II includes localized tenderness and partially torn MCL and posterior oblique fibers, and grade III is defined as complete disruption and instability with applied valgus stress\textsuperscript{3}. Tears are further graded by valgus laxity with 1+ encompassing tears that reveal 0-5 mm laxity with a firm endpoint\textsuperscript{25} on physical exam, 2+ with 6-10 mm laxity with a firm endpoint\textsuperscript{25}, and 3+ > 10 mm laxity with a soft endpoint (see Table 1)\textsuperscript{3,6,14,18,25,26}. In practice, a functional grading system is often implemented which requires valgus stress testing at 0 and 30 degrees. If minimal laxity and pain are present with valgus stress at 0 and 30 degrees, a grade I tear is indicated\textsuperscript{25}. Findings consistent with a grade II injury are laxity at 30 degrees but stability at 0 degrees; grade III findings include laxity at both degrees\textsuperscript{25}. This pattern of laxity is often indicative of a concomitant cruciate ligament injury. In the setting of ligamentous laxity, it is important to confirm intact neurovascular status with pedal pulses or ankle-brachial index\textsuperscript{25}.

After physical examination indicates a MCL tear, imaging follow-up is recommended especially in the acute setting\textsuperscript{25}. Studies indicate that the acute phase of injury can limit detection of the classic findings for MCL tear during physical examination\textsuperscript{25}, and imaging can then confirm grade of tear, combined ligament injuries, avulsions or fractures, and other meniscal or chondral damage\textsuperscript{25}. Imaging modalities may include radiographs and MRI. The recommended radiograph is a weight-bearing standard
four view knee series with anteroposterior and lateral being the minimum views required\textsuperscript{14,17,18,25}. Isolated MCL tears often result in normal knee radiographs, but joint widening findings or asymmetry sometimes indicate multiligamentous involvement\textsuperscript{25}. Additionally, radiographs can detect avulsion fracture or other acute bony injury.

MRI diagnosis of MCL injury is reported to be 87\% accurate which challenges the current clinical gold standard of diagnosis\textsuperscript{9,21}. Grade I injury on MRI is typically defined as an intact MCL with microscopic tears of surrounding individual fibers, grade II involves visible changes or high intrasubstance signal to the MCL, and grade III represents complete ligamentous discontinuity with laxity or waviness\textsuperscript{21}. Visualization of both the superficial and deep MCL are best seen on T1 and T2 weighted images on the coronal series\textsuperscript{10}.

Table 1: Classification of MCL Tears by Grade

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Grade I</td>
<td>Localized tenderness without instability Firm endpoint</td>
</tr>
<tr>
<td>Grade II</td>
<td>Localized tenderness and partially torn medial collateral and posterior oblique fibers Firm endpoint</td>
</tr>
<tr>
<td>Grade III</td>
<td>Complete disruption; instability with valgus stress Soft or no endpoint</td>
</tr>
<tr>
<td>Clinical Subjective</td>
<td>3-5 mm laxity</td>
</tr>
<tr>
<td>1+</td>
<td>6-10 mm laxity</td>
</tr>
<tr>
<td>2+</td>
<td>&gt;10 mm laxity</td>
</tr>
</tbody>
</table>

1.1.5 Medial Collateral Ligament Treatment

The treatment of MCL sprains, especially for grade I and II tears, is mainly conservative\textsuperscript{2,3,7,11,12,17}. Isolated grade I tears can be treated effectively with rest, ice, compression, and elevation especially during the first 72 hours\textsuperscript{6}. Non-steroidal anti-inflammatory drugs can be used to alleviate symptoms\textsuperscript{6}. An example rehabilitation
protocol includes use of a hinged knee brace to protect against valgus stress and early emphasis on range of motion\textsuperscript{6}. The goal range of motion before progression to walking outdoors or on a treadmill is 90 degrees with progression to running at 75\% of maximum speed\textsuperscript{6}. Full resolution of pain is a common marker of recovery. Treatment of grade II injuries can be similar to that of grade I with return to activity being allowed once quadricep strength is 90\% or greater than the contralateral quadricep and regular activity or agility testing does not cause pain\textsuperscript{6}.

Treatment of grade III MCL tears becomes more complicated as there is the potential for more severe instability, entrapment, or avulsion, all of which have been proposed as criteria for surgical intervention\textsuperscript{14}. Some guidelines suggest that the stability of the sprain is a key factor in the decision between surgical and conservative treatment\textsuperscript{14,17,18}. Studies have also shown that in grade III MCL sprain, the risk of additional ligament injury is up to 78\% and commonly involves the ACL\textsuperscript{11,15,17,27}. Of this group of patients, a combined MCL-ACL injury accounts for over 90\% of medial ligament injuries\textsuperscript{11}. In this case, usual practice is to delay surgery for five to eight weeks to allow the MCL an opportunity to heal before ACL reconstruction\textsuperscript{14,18}. The decision becomes whether to simultaneously repair the MCL during ACL reconstruction surgery. One recent study found no significant pain difference in patients who underwent simultaneous MCL repair and ACL reconstruction versus patients who only underwent ACL reconstruction while another study found a worse outcome with concomitant repair of both ligaments\textsuperscript{16,28}. The importance of these studies is that they support conservative treatment for isolated grade III MCL tears.
Some studies argue that grade III isolated tears without evidence of significant valgus instability are candidates for conservative treatment and have even shown superiority to operative treatment\textsuperscript{9,18,28,29}. This includes functional rehabilitation, physical therapy, and use of a hinged brace\textsuperscript{14,17}. There has also been a transition away from prolonged immobilization towards crutches and early mobilization\textsuperscript{18,22,28-31}. The rationale is that this approach improves longitudinal alignment and concentration of cells and collagen\textsuperscript{4,10,18}. The goal of physical therapy is to restore quadriceps function, improve knee range of motion, and resolve knee edema\textsuperscript{18}. For the first three to four weeks, exercises include the use of a stationary bike and exercises that do not require lateral movements to protect the knee from valgus stress\textsuperscript{18}. When the clinical exam indicates healing by decreased pain and laxity with valgus stress testing, return to full activity or sport becomes the goal\textsuperscript{18}. Even with physical therapy efforts, grade III injury recovery averages five to eight weeks\textsuperscript{7,18,29}. Additionally, clinicians worry about failed conservative treatment of grade II and III MCL tears in some cases can leading to persistent medial instability, weakness, and osteoarthritis\textsuperscript{17}.

1.1.6 Benefits of Platelet-Rich Plasma

The basis for the benefit of platelet-rich plasma (PRP) is that it is an autologous concentration of platelets above that which is normally in whole blood\textsuperscript{24,32-34}. This is achieved by centrifuging whole blood to separate it into components based on density\textsuperscript{33,34}. The resulting platelet layer is located in highest concentration in the plasma and includes an increased concentration in of various growth factors, all of which enhance the body’s natural healing process\textsuperscript{33-36}. PRP has multiple components including platelets, leukocytes, and red blood cells\textsuperscript{33}. When platelets come into contact with an
injured area during normal tissue healing, they degranulate and release growth factors\textsuperscript{37}. These numerous growth factors upregulate protein metabolism, stimulate neovascularization, and are proposed to accelerate healing\textsuperscript{24,34,37}. Additionally, growth factors synthesize collagens and over 300 extracellular matrix anabolic proteins\textsuperscript{38}. The process of preparing a PRP injection results in a three to fivefold increase in the concentration of platelets and therefore growth and differentiation factors in comparison to the body’s natural environment.\textsuperscript{24,34} This heightened concentration theoretically could be the difference in complete versus incomplete recovery from an acute injury.

The majority of PRP applications in orthopaedic injuries has focused on tendon injuries and tendinopathies and have shown evidence that PRP is effective in the treatment of tendinopathy\textsuperscript{37,39,40}. To date, randomized controlled trials investigating the effect of PRP on MCL pathology has not been conducted. However, several case studies have reported positive results in terms of decreased time lost to injury and return to play\textsuperscript{41-43}. Augmentation with PRP has seen success in other populations, and although it has been applied for MCL tears in practice, a confirmatory trial has not been conducted.

1.2 STATEMENT OF THE PROBLEM

The standard of care for isolated medial collateral ligament tears is a physical therapy regimen emphasizing early range of motion and progression to weight bearing exercises\textsuperscript{12}. This type of functional rehabilitation is generally effective for grade I and II tears as evidenced by patient outcomes and return to activity at an average of two to three weeks\textsuperscript{6,12}. Still, more severe grades of MCL tears have a longer recovery and carry the risk of residual medial instability with failed physical therapy. The treatment of grade III injuries is also a discussion of non-operative versus operative treatment\textsuperscript{6}. Non-operative
treatment of grade III tears has been successful but results in a longer loss of time due to injury than grades I or II tears\textsuperscript{15,28,29}. Additionally, grade III MCL injuries have a high incidence of concomitant ligament damage, with ACL rupture being the most common\textsuperscript{15}. Surgical reconstruction of the ACL is the standard of care in high-demand athletes, but management of combined MCL-ACL injuries remains controversial\textsuperscript{15,44}. A recent study showed no significant difference in outcomes between conservative versus operative management of the MCL in the setting of ACL reconstruction which, in turn, supports non-operative treatment of isolated MCL tears\textsuperscript{15}.

Platelet-rich plasma injections have been proposed to augment the body’s natural healing process\textsuperscript{24}. Application of PRP injections in the MCL injured population has three potential benefits. The first is that superficial MCL is abundantly vascularized, follows the classic model of healing, and would therefore potentially benefit from platelet-rich plasma by the addition of a high concentration of the biological components needed for tissue healing\textsuperscript{3}. Secondly, MCL tears that involve the deep MCL, especially those that are not clinically discovered, can cause lingering pain. A PRP injection would flood the MCL area and possibly allow for more tissue healing of the deep MCL. Finally, although our study will include a broader population of patients with MCL injuries, athletes at various levels who are focused on returning to play as soon as possible would particularly benefit from a conservative treatment that decreases pain and promotes faster healing.

To date, two case reports of elite athletes with acute MCL sprain have described favorable results with PRP injection quantified by time to return to play\textsuperscript{41,43}. However, there have been no randomized studies investigating the benefit of platelet-rich plasma on recovery from MCL injury. There is a need for a blinded randomized controlled trial
investigating PRP in the setting of MCL tears. Our study will examine platelet-rich plasma as an adjuvant to physical therapy in comparison to a control group receiving a placebo injection for isolated grade II and grade III MCL injuries, given the longer recovery time associated with a more severe tear. Successful conservative therapy of MCL injury avoids necessity for a surgical intervention and decreases time lost to injury. The potential for platelet-rich plasma to contribute to the success of conservative therapy will potentially provide a great benefit to our study population.

1.3 GOALS AND OBJECTIVES

The proposed study is a randomized, double blind, controlled trial examining the efficacy of a platelet-rich plasma injection for patients with isolated grade II and grade III medial collateral ligament tears. Both groups will undergo standard physical therapy for MCL tears with emphasis on range of motion and early weight bearing. The goal of this study is to determine whether platelet-rich plasma is an effective adjuvant to conservative treatment for acute isolated grade II and grade III MCL tears. The main objective of this study is to determine the mean difference for a group of patients treated with PRP between baseline Visual Analog Scale (VAS) scores and scores at two, four, and six weeks compared with pain scores for a placebo injection group. Our study will evaluate the efficacy of conservative treatment for more severe grades of MCL tears (II and III) and investigate platelet-rich plasma as an adjunct to non-operative treatment.

1.4 HYPOTHESIS

Patients with isolated grade II or III medial collateral ligament tears aged 18-45 who are treated with platelet-rich plasma as an adjuvant to standard physical therapy will have a statistically significant mean difference in Visual Analog Scale scores from
baseline to two-, four-, and six-week follow-up in comparison to patients treated with a placebo injection\textsuperscript{c} and standard physical therapy\textsuperscript{d}. The expected clinically significant effect size expected to be -3.6 +/- 2.3 at six-week follow-up.

1.5 DEFINITIONS

a. Platelet-Rich Plasma: Platelet-rich plasma (PRP) is an autologous concentration of human platelets obtained by a venous blood draw, a centrifugation process to separate out the plasma, and preparation as in injection with a three to fivefold increase in growth factors to augment the body’s classic model of healing\textsuperscript{24}. PRP injections are also categorized by the abundance of neutrophils; denoted leukocyte-rich (LR-PRP) for PRP preparations with an above average number of leukocytes, or leukocyte-poor (LP-PRP) if below the average number of leukocytes\textsuperscript{24}.

b. Visual Analog Scale (VAS): The Visual Analog Scale (VAS) is a 10 cm number line beginning at 0 where the left endpoint is designated “no pain” and the right endpoint is “worst pain imaginable”. The patient selects a point along the line that corresponds to the pain he or she is feeling at the time of completion.

Figure 1: Visual Analog Scale (VAS)

\begin{center}
\includegraphics[width=0.5\textwidth]{visual_analog_scale.png}
\end{center}

\begin{itemize}
\item No pain
\item Worst pain imaginable
\end{itemize}

c. Placebo injection: A standard placebo injection is 0.9\% normal saline prepared in with the same protocol as the intervention injection.

d. Standard physical therapy: Standard physical therapy for medial collateral ligament tears include quadriceps and leg muscle strengthening and early range of motion protocols followed by a progressive return to functional and sport-specific movements in four to six weeks.
1.6 REFERENCES


CHAPTER 2: REVIEW OF THE LITERATURE

2.1 INTRODUCTION

A review of the literature was conducted between December 2019 and May 2020 using Pubmed, Scopus, Ovid, ScienceDirect, and Cochrane Medical Library. The MeSH terms used to search these databases included “collateral ligaments/injuries”, “ligaments, articular/injuries”, “ligaments, articular/surgery”, “platelet-rich plasma”, “athletic injuries/therapy”, “knee injuries/therapy”, “patellar ligament/injuries”, “tendinopathy/therapy”. Other search terms included medial collateral ligament, grade III medial collateral ligament, medial collateral ligament repair, patellar tendinopathy, Achilles tendinitis, lateral epicondylitis, muscle tear, osteoarthritis, and return to play.

The literature review showed support for the potential benefits of PRP therapy for various orthopaedic injuries but also revealed multiple studies lacking a true control group. Although a population that would seemingly benefit from PRP therapy, there have only been three case reports of the use of PRP in patients with MCL injuries and no published randomized controlled trials. The few case studies indicated a positive benefit, but in order to evaluate the efficacy of platelet-rich plasma for the treatment of MCL injuries, a well-designed, randomized, double-blind, placebo-controlled trial is needed.

2.2 REVIEW OF EMPIRICAL STUDIES

2.2.1 Platelet-Rich Plasma Treatment

In orthopaedics and sports medicine, the basic science of PRP has been an attractive treatment option, with applications in repairing injured tissue, treating degenerative disorders, and accelerating return to sport\(^1\). The applications of PRP range from chronic conditions to surgical augmentation, tendinopathies, sprains, and tears.
Although there have been no published trials on PRP treatment for the MCL, many studies investigating PRP in similar soft tissue injuries have showed their efficacy in improving pain and decreasing time lost due to injury. However, many studies lacked comparison to a true control group and, due to various limitations including lack of blinding, some studies have found no benefit to the application of PRP.

2.2.1.1 Tendinopathies

Perhaps the most widely studied application of PRP has been to treat tendinopathies including patellar tendinopathy, Achilles tendinopathy, rotator cuff tendinopathy, and lateral epicondylitis. In reviewing the literature, we grouped studies based on primary outcome, comparison group, and presence or absence of a control group. We began by examining a recent metanalysis by Fitzpatrick et al. who included ten randomized controlled trials that found significant results of PRP therapy for Achilles tendinitis and patellar tendinopathy.

A closer look at two studies included in this metanalysis, while notable due to the positive trending of their respective outcome measurement, lacked comparison to a true control group and instead chose to compare results of PRP treatment to another current treatment for the particular tendinopathy. Vetrano et al. investigated weekly PRP injections for two weeks in treatment of patellar tendinopathy. The comparison group was patients who underwent electric shock wave therapy (ESWT). They found that the PRP injection group showed significantly better improvement in VAS than patients randomized to the ESWT group at six months, $2.4 \pm 1.9$ versus $3.9 \pm 2.3$ ($p = 0.028$), and twelve months, $1.5 \pm 1.7$ versus $3.2 \pm 2.4$ ($p = 0.009$)\textsuperscript{4}. The study also showed decreased VAS scores in the PRP group from a baseline of $6.6 \pm 1.8$ to $2.3 \pm 1.9$ at 6 months and
1.5 ± 1.7 at 12 months. Another study by Dragoo et al. comparing PRP for patella tendinopathy with dry needling and found a significant decrease in VAS pain score by 2.4 ± 2.1 points at twelve weeks (p = 0.008) and by 2.6 ± 1.7 (p = 0.003) at twenty-six weeks\(^5\). They did not find a significant difference between the dry needling group and the PRP group at any time interval, highlighting the need for comparison to a true control group of standard physical therapy.

A nonrandomized controlled trial by Filardo et al. selected patients for a PRP group and a control group based on whether the patient had or had not received prior treatment for patellar tendinopathy\(^6\). They found a significant decrease VAS scores in patients refractory to treatment from baseline of 6.6 ± 1.4 to 4.3 ± 1.7 (p = 0.002) to 3.1 ± 1.2 (p = 0.02) at the six month follow-up for patients in the PRP group\(^6\). In comparison, the control group had a decrease in pain level from 6.7 ± 1.5 to 3.2 ± 2.4 (p = 0.001)\(^6\).

Aside from the VAS scale, pain and disability from patellar tendinopathy is also assessed by the Victorian Institute of Sports Assessment-Patellar questionnaire (VISA-P) (See Appendix G). A similar unblinded prospective cohort study by Gosens et al. found that a single PRP injection in patellar tendinopathy resulted in an improvement in VISA-P scores from 39.1 ± 16.6 to 58.6 ± 25.4\(^8\). The group was compared to patients who had either surgery or a prior injection to the injured knee who did not exhibit statistically significant improvement in VISA-P scores following physical therapy (p = 0.060)\(^8\). Limitations of these studies include nonrandomization and the unblinded protocol respectively.

Achilles tendinopathy is another application of PRP with a similar population to the focus of our study as 52% of lifetime prevalence of Achilles tendinopathy is in former
runners. In contrast to studies investigating patellar tendinopathy, the literature for Achilles tendinopathy has more conflicting results. A study by Filardo et al. found that, after a single PRP injection, Victorian Institute of Sports Assessment - Achilles (VISA-A) (see Appendix G) scores improved from a baseline of 49.9 ± 18.1 to 62.9 ± 19.8 (p = 0.002) at two months with further improvement to 84.3 ± 17.1 (p < 0.0005) at six months. Another study by Boesen et al. showed that PRP or high-volume corticosteroid injections are more beneficial than standard physical therapy exercises in terms of decreased VAS measures, but the results failed to demonstrate a significant difference between PRP and corticosteroid injections. Several other case series have found improvements on VISA-A scores with the use of PRP for Achilles tendinitis, but they note that further randomized control trials need to be conducted to explore the promising results.

In contrast, a few randomized control trials were unable to find a significant effect of a PRP injection versus a saline injection with the primary outcome of the VISA-A scores. A study by de Vos et al. that was included in Fitzpatrick et al.’s metanalysis found that VISA-A scores improved significantly after twenty-four weeks in the PRP group (by 21.7 points (CI, 13.0-30.5) whereas the placebo saline injection group decreased by 20.5 points (CI, 11.6-29.4). After regression controlling for predictors of VISA-A scores, this difference in scores was not significant. Rationales for these conflicting results again include the lack of comparison to a true control group in the case of the Boesen et al. study, lack of randomized controlled trials, and randomized study protocols, and the more chronic nature and duration of symptoms in patients with Achilles tendonitis.
PRP therapy has also been investigated for treatment of lateral epicondylitis, commonly known as “tennis elbow”. Similar to the literature on patellar tendinopathy, many studies lack comparison to a true control group. A double-blind randomized control trial by Gosens et al. compared a PRP injection group and a corticosteroid injection group. The corticosteroid injection group reported lower VAS scores at four and eight weeks but the PRP group overtook these scores and had a significantly reduced VAS measure at twenty-six weeks in comparison to the corticosteroid group\textsuperscript{19}. A similar study by Peerbooms et al. found that the PRP group reported a mean VAS improvement of 44.8\% (70.1 to 38.7), whereas the corticosteroid group reported a 32.8\% (65.8 to 44.2)\textsuperscript{20}. Krogh et al. then seemingly addressed this issue of a lack of control group by comparing three groups: PRP, glucocorticoid, or saline and found no statistical difference between pain reduction scores at three months\textsuperscript{21}. The mean difference of pain reduction in the PRP group in comparison to saline group was found to be significant (-2.7 [95\% CI, 28.8 to 3.5])\textsuperscript{21}. Importantly, the study experienced significant drop-out and thus the length of the outcome was dramatically reduced from twelve to three months to conserve the power of the study. Additionally, 42\% of the patients stated that their daily work was the cause of their lateral epicondylitis, and a rest period after injection was not possible in many cases.

Studies investigating PRP for the treatment of various tendinopathies in both upper and lower extremities have generally concluded favorable results. Still, some studies were unable to conclude a significant result. Multiple confounding variables likely contribute to the inconsistencies in the literature (see section 2.3). Further, a common theme for the above articles was the presence of a comparison group that was also a treatment for the particular tendinopathy, or no comparison group at all. Without a
true control group of a placebo intervention or simply standard physical therapy, it is difficult to delineate the true effect size of PRP therapy.

2.2.1.2 Acute Muscle Tears and Sprains

Because we will be studying a population with an acute injury, we also reviewed the literature on the use of PRP in acute muscle strains and ligament sprains. A randomized controlled trial by Hamid et al. investigated grade IIA acute hamstring tears in athletes and PRP as an adjuvant therapy to physical therapy\textsuperscript{22}. The mean return to play for the PRP group was $26.7 \pm 7.0$ days; the mean return to play for the control group was $42.5 \pm 20.6$ days\textsuperscript{22}. This is a seemingly large effect, but the control group did not have their blood drawn meaning patients were likely aware of their group allocation\textsuperscript{22}. Shortly after this study was published, a double-blind randomized controlled trial by Rossi et al. examined PRP injection in conjunction with a physical therapy regimen versus a physical therapy regimen alone on a group of hamstring, quadriceps, and gastrocnemius tears and found a significant reduction in return to play of 4 days\textsuperscript{23}. The mean time to return to play was $21.1 \pm 3.1$ in the PRP group and $25.5 \pm 2.8$ days for the control group\textsuperscript{23}. In the PRP group, VAS was measured as a secondary outcome and was found to be significantly decreased from $5.9 \pm 1.1$ to $4.7 \pm 1.2$ (beta regression coefficient = -0.272, $p = 0.019$)\textsuperscript{23}. The results meant that an athlete from the treatment group was able to play in one more game than athletes in the control group\textsuperscript{23}. Additionally, since the VAS pain scores were lower at all points during the study, patients in the treatment arm could progress faster through the rehabilitation program\textsuperscript{23}.

The application of PRP is particularly beneficial for elite athletes due to their need for a rapid return to play. Studies have asserted faster return to play with PRP therapy for
ulnar collateral ligament (UCL) tears in elite baseball players\textsuperscript{24} and in athletes with high ankle sprains\textsuperscript{25}. However, we found that the issue of a lack of control group in the literature investigating PRP therapy to especially prevalent in studies examining an athletic population. A rationale for this might be that due to the need for rapid rehabilitation, athletes might not agree to a randomized control trial in which they might receive a placebo injection. Podesta et al. examined PRP for partial UCL tears and found that among baseball, softball, tennis, and volleyball patients who have sustained partial UCL tears, the average return to play was $12 \pm 3$ weeks\textsuperscript{26}. Another study by Retting et al. notes that at 3 months after a UCL tear, only 42 percent of patients are fully recovered which suggests the potential benefits of PRP for UCL tears even if direct comparison to a control group has not yet been made\textsuperscript{27}. Another study by Laver et al. examined high ankle sprains in sixteen elite athletes and found that after a single PRP injection, the mean return to play was $40.8 \pm 8.9$ days in the PRP group and $59.6 \pm 12.0$ in the control group ($p = 0.006$)\textsuperscript{25}. Although promising, the study does note that the participants were not blinded, which could have led to information bias and resulted in a seemingly higher effect of the PRP injection\textsuperscript{25}.

2.2.1.3Other Chronic Conditions

Although the acute MCL tear population is generally younger than patients with primary osteoarthritis of the knee, several high-quality studies have been conducted in this population. Still, as a common theme to the available literature on PRP therapy, many studies compared PRP to an injection of hyaluronic acid (HA) which is a common treatment in osteoarthritis and cartilage degeneration instead of to a placebo injection or other true control group\textsuperscript{28}. The primary outcomes included the International Knee
Documentation Committee score (IKDC) and the Western Ontario and McMaster Universities Osteoarthritis Index\textsuperscript{29} (WOMAC) (See Appendix G for full forms of both scales)\textsuperscript{28} and found significant improvement at six and twelve months in comparison to viscosupplementation\textsuperscript{28,30-34}.

In contrast, a recent double-blind randomized control trial by DiMartino et al. comparing PRP and hyaluronic acid injections for primary osteoarthritis found no superior improvement in the PRP group over the HA group\textsuperscript{35}. However, the study lacked a true control group which was addressed by another recent study by Lin et al. comparing three groups: PRP, HA, and a normal saline injection\textsuperscript{31}. As with the other study, no significant difference was found between the PRP and HA groups in terms of IKDC scores at any point during the study\textsuperscript{31}. However, the study found a significant improvement in the PRP group over the normal saline group throughout the study duration. The baseline IKDC score for the saline injection group was 33.3 ± 10.52 in comparison to that of the PRP group, which was 35.71 ± 13.77. At 6 months, the scores were 34.2 ± 11.11 and 47.33 ± 16.24 respectively\textsuperscript{31}.

\textbf{2.2.2 Platelet-rich Plasma Improves MCL Healing}

Despite the relatively robust literature for platelet-rich plasma in orthopedic injuries, there have been no prospective randomized control trials testing the efficacy for recovery from MCL tears. A metaanalysis analyzing patellar tendinopathy and medial collateral ligament trials for PRP found only a case study of a professional soccer player who was treated with three injections of PRP for an isolated acute grade III MCL tear that occurred during an in-season match\textsuperscript{36}. The decision was made to inject PRP weekly until the patient was pain-free. The treatment protocol resulted in an mere 18-day loss of time.
due to MCL injury and a reported completion of a full soccer match at day 25\textsuperscript{37}. The authors note the limitations of a single case report but emphasized the benefits of PRP for this athlete and encourage further prospective trials to understand the true effect size of PRP for isolated MCL sprains\textsuperscript{37}.

The only other available literature on PRP for MCL sprains is a case report describing three patients with a history of grade I or II MCL sprains and persistent pain\textsuperscript{38}. Each patient’s injury mechanism was contact during a recreational football game with a mean time before starting PRP therapy of ten months\textsuperscript{38}. Each tear was confirmed on MRI to have residual increased signaling in the superficial or deep MCL. The researchers prepared a leukocyte-reduced PRP injection for each patient and patients then were instructed to be non-weight-bearing for a week after the procedure\textsuperscript{38}. A post-treatment MRI was obtained from each patient which revealed recovery of the MCL. Although the study mentions that this indicates that PRP seemed to accelerate healing of the MCL in the study patients, they note that further randomized studies with a larger sample size are needed to further evaluate this relationship\textsuperscript{38}.

The above case reports all deliver promising results for both chronic and acute injuries; however, it is difficult to draw conclusions based on any one single case. Additionally, publication bias might be a factor as it stands to reason that a case where a patient was treated with PRP but did not return to play is not likely to be published. Therefore, although there seems to be a potential benefit for treatment of MCL tears with PRP, a randomized controlled trial powered to detect a difference in effect between an intervention group and a control group is required to further investigate this relationship.
2.3 REVIEW OF STUDIES TO IDENTIFY CONFOUNDING VARIABLES

There are multiple potential confounding variables within the procedure for preparation of PRP. The first example is the various PRP kits that are available. Studies have used a wide range of these kits, including: Recover System from Biomet\textsuperscript{8,19}, MyCells Autologous Platelet Preparation System\textsuperscript{4}, GPS III\textsuperscript{5}, Arthrex Double Syringe System\textsuperscript{9,39}, as well as institution-specific PRP preparation\textsuperscript{6,11,17,40}. A study by Degen et al. compared commercial separation systems for PRP injections to investigate differences between different kits as potential confounding variables but found no significant difference in platelet concentrations between the five kits included in the study. However, the concentration of white blood cells, neutrophils, red blood cells, and pH were variable and in some cases statistically significant\textsuperscript{41}. A limitation of this study was the small sample size and the inclusion of only five preparations when dozens exist.

Multiple studies note that there are several aspects of PRP treatment that have not been rigorously studied, including the volume of the injection, the inclusion or exclusion of leukocytes, the most effective preparation, injection technique, depot versus multiple depots, and single application versus series of injections\textsuperscript{8,42}. A study by Dallaudiere et al. discusses the potential confounding variable of differing platelet counts that are procured from the centrifuging process across preparation kits\textsuperscript{43}. The study discusses the importance of quantifying platelet and leukocyte counts for standardization and notes that much of the literature does not disclose this information\textsuperscript{42}. Our literature review was consistent with this assertion; some of the analyzed studies did note the concentration of platelets in comparison to whole blood and the average number of platelets injected\textsuperscript{6,26,43}, but the majority did not\textsuperscript{5,8,9,17,18,21,39}. De Vos et al., who examined Achilles tendinopathy,
noted that their study was unable to quantify the amount of platelets that were injected after an in-house preparation of the plasma\textsuperscript{17}. Notably, their study did not find PRP to have a significant effect on VISA-A scores, therefore raising the issue of whether the platelet concentration was less than the optimal level.

Another study investigating the most effective preparation by Filardo et al. who examined PRP injections in osteoarthritis, compared the preparation of the injection: single versus double-spinning\textsuperscript{44}. The study assigned 72 patients to a single spun PRP injection, and 72 to a double-spun injection and found that there was no significant difference between the IKDC and VAS scores at two, six, and twelve-month follow-up appointments\textsuperscript{44}. This addresses a potential confounding variable of differing preparations of the injections on results, but the results of this study are evidence that the clinical significance of slightly differing preparations is not enough to skew the study findings. The authors also note that some studies utilize leukocyte-rich injections, which is defined as a preparation containing higher white blood cell concentrations than that of whole blood\textsuperscript{45}, while others opt for leukocyte-poor injections. In general, the study states that better results are found with leukocyte-poor injections for osteoarthritis with the rationale that they contain proteases and reactive oxygen species which exacerbate an already inflammatory pathology\textsuperscript{44}. In contrast, some studies consider the fact that leukocytes are a source of cytokines and enzymes that might be important in promoting inflammation and subsequently improved tissue healing as the rationale for a leukocyte rich injection, particularly in tendinopathies\textsuperscript{44}.

Additionally, several studies use a single injection protocol,\textsuperscript{5,6,9,23,25,38,46-50} whereas others use multiple injections\textsuperscript{37,39,51,52}. Two retrospective studies have found that in...
comparison of single versus multiple PRP injections, there was no significant difference at the respective post-injection intervals\textsuperscript{33,39}. However, a study by Gormeli et al. compared single versus multiple PRP injection in early versus advanced osteoarthritis and found that VAS scores for patients with early osteoarthritis improved significantly more with multiple PRP injections versus a single injection\textsuperscript{52}. The differing protocols for PRP injection is further outlined in Section 2.4.3 and Table 2.

Aside from confounding variables associated with PRP injection preparation and administration, multiple confounding variables could affect the healing process of MCL tears including age, sex, body mass index, days between injury and intervention\textsuperscript{53}, circumstance of injury, activity level, and post-treatment rehabilitation protocols\textsuperscript{5,9,23,25,52}. In particular, our literature review revealed the average age of study participants to be widely variable. Studies investigating PRP for patellar tendinopathy have an average age range of 27-30\textsuperscript{4,6,8,39} whereas studies for Achilles tendonitis average at 40\textsuperscript{9,11,13,17,18}. The average age of study participant in the lateral epicondylitis patients is 45-50\textsuperscript{19-21}. Studies have stated that older subjects might be less responsive to the potential benefits of PRP treatment\textsuperscript{17}. This may be in part to advancing age typically corresponding to more advanced chronic conditions, and therefore beyond the point where increased concentration of the body’s natural healing process could significantly recover the condition. An example of the importance of this confounding variable is the two studies on Achilles tendonitis by de Vos et al. and de Jonge et al. were unable to conclude that PRP had a significant improvement on VISA-A scores. Notably, the mean ages of the study participants were significantly older, 49.7\textsuperscript{18} and 49\textsuperscript{17} years old respectively.
Finally, the standard of care for conservative treatment of tendinopathies, sprains, and tears usually involves a course of physical therapy tailored to the respective injury. Studies including a rehabilitation protocol often discussed whether there was adherence to the physical therapy regimen, especially if the program was unsupervised. Fitzpatrick et al. who studied PRP and gluteal tendinopathy stated that participants were evaluated at six weeks in order to clear the patient for a progressive walking program with the previous six weeks acting as the preparation for this advancement. They concluded that there was complete adherence to the protocol thus eliminating it as a potential confounding variable. Further, a study by Hamilton et al. investigating hamstring strains and PRP treatment was able to use a single-center rehabilitation program and effectively monitor compliance. However, Boesen et al. noted that only 70% of participants performed the recommended exercises that were part of the intervention and control treatment protocol for Achilles tendonitis.

2.4 REVIEW OF RELEVANT METHODOLOGY

2.4.1 Study Design and Setting

Multiple randomized controlled trials have been conducted to examine the effects of PRP in comparison to current therapy in a variety of orthopaedic conditions. Studies investigating patellar tendinopathy are more similar to our proposed study population, but our literature review revealed more prospective double-blind, randomized, placebo-controlled trials in the osteoarthritis population. Further, trials employing a truly controlled placebo group as the comparison group are limited. Previous case reports have shown favorable results for PRP treatment in MCL tears but no prospective studies have been published which indicates the need for a double-
blind, randomized controlled trial to determine the effect of adjuvant of PRP with standard physical therapy on the recovery of MCL tears with the use of a placebo-controlled group of a placebo injection and physical therapy for comparison.

Trials generally used a single center design because of sample size and desired standardization of the injection protocol. We will also be using a single-center study design. Participants will be recruited using convenience sampling with computer-generated simple randomization, similar to other studies.

2.4.2 Selection Criteria

2.4.2.1 Inclusion

Available literature on treatment of MCL tears was examined to determine the inclusion and exclusion criteria for our proposed study. Inclusion criteria in studies similar in population to our proposed study consistently adhered to the grading system for MCL tears outlined in Section 1.1.4 (see Table 1). Our study will include grade II and grade III tears. The rationale for the decision to include both grade II and III tears is the broad description of grade II injuries which can range from minimal signal changes in the MCL to near complete tears.

Other important inclusion criteria for our study were developed using exclusion criteria from studies investigating surgical intervention for grade III MCL tears. Zhang et al. conducted a study investigating simultaneous reconstruction of the MCL and ACL and included combined ACL-MCL laxity, subjective medial instability with a grade II or III MCL injury (medial joint opening > 5 mm based on radiographs compared with the contralateral knee). Therefore, our inclusion criteria will include isolated grade II or III MCL injuries without medial instability or with medial instability < 5 mm.
2.4.2.2 Exclusion

The most important exclusion criterion for our study is candidacy for surgical intervention. In a review of the literature, this included grade III MCL tears with associated avulsion at the tibial insertion for which surgical intervention has yielded positive results\textsuperscript{58-60}. Similarly, combined MCL-ACL injury in active adults is often surgically managed\textsuperscript{60}. Further, multi-ligament injury is common in higher grade MCL tears,\textsuperscript{61} but, for the purposes of our study, it would be difficult to isolate pain specific to the MCL injury. This exclusion criterion is consistent with Zhang et al. who excluded posterior cruciate ligament (PCL) injure or posterolateral corner injury\textsuperscript{57}. The study also excludes active infection, malalignment, or any previous ipsilateral knee surgery as any of these conditions might delay healing\textsuperscript{57}. Our study will also exclude previous ipsilateral knee surgery.

Studies on PRP for other orthopaedic injuries, including lateral epicondylitis\textsuperscript{62} and high ankle sprains, reported additional exclusion criteria that is applicable to our study. Mishra et al., who examined lateral epicondylitis and PRP, excluded pregnancy, history of anemia, history of bleeding disorder, Hemoglobin < 11 g/dL, Hematocrit < 33\%, platelet count outside of the normal range from 150-400 x 100/uL, participation in a workers’ compensation program, and local steroid injection within 6 weeks to the ipsilateral elbow\textsuperscript{62}. Rowden et al., who examined PRP and high ankle sprains, excluded current anticoagulation or antiplatelet therapy, as well as a history of thrombocytopenia\textsuperscript{49}. A study by Smith et al. examining osteoarthritis and PRP injections excluded patients with clinically 3+ effusions, previous surgery of the target knee within the past six months, positive pregnancy test, or intent to become pregnant during treatment period,
rheumatoid arthritis, history of infection with the target joint, and participation in any experimental device or drug study within one month before screening visit. Our study will similarly exclude previous surgery within the past six months and a history of infection of the ipsilateral knee.

2.4.3 Intervention

PRP injections have shown promise in orthopaedics and sports medicine in improving recovery from tendinopathy, acute muscle tears and sprains, ligament sprains, and osteoarthritis and will be the intervention in the proposed study.

2.4.3.1 Dose

Our review of the literature revealed a widely variable dose and preparation protocol among preparation kits utilized by individual studies. Currently, there is no consensus on a superior method of preparation or on optimal amount of infiltration. We therefore focused on randomized controlled trials to compare the different dosages and protocols and organized our findings in Table 2 below. One important finding during our search of the literature revealed that many studies did not report the increase in platelet concentration from baseline that was being injected. The optimal increase in concentration of platelets for effective therapy is unknown, but studies finding significant benefit with PRP obtained a range of $1.81 \pm 0.34$ times baseline to $4.6 \pm 1.4$ times baseline concentration.

The literature reflects the heterogeneity of the proposed optimal volume of PRP. One study noted that there is no consensus on the optimal amount of PRP and injected the volume equivalent to the volume of the muscle injury. Other studies used 3 mL, 4 mL, and 5 mL injections. Additionally, treatment options varied from a one-time
injection\textsuperscript{5,6,9,23,38,46-50} to a series of 2-3 treatments\textsuperscript{4,31,35,37,39,51,52}. Notably, ultrasound guidance was almost universally used\textsuperscript{4,5,23,25,49}.

Table 2: Dosages and Protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Injury</th>
<th>Preparation Kit</th>
<th>Peripheral Draw</th>
<th>Anti-Clotting/ Additions</th>
<th>Centrifuge Speed</th>
<th>Resulting Injection</th>
<th>Platelet Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dragoo et al.\textsuperscript{5}</td>
<td>knee</td>
<td>GPS III (Biomet)</td>
<td>55 mL</td>
<td></td>
<td></td>
<td>6 mL LR-PRP</td>
<td></td>
</tr>
<tr>
<td>Vetrano et al.\textsuperscript{4}</td>
<td>knee</td>
<td>MyCells</td>
<td>10 mL</td>
<td>Acid-citrate-dextrose</td>
<td>1500g</td>
<td>2 mL LR-PRP (22-gauge)</td>
<td>Mean 0.89-1.1 x 10\textsuperscript{9} mL</td>
</tr>
<tr>
<td>Filardo et al.\textsuperscript{6}</td>
<td>knee</td>
<td>Institution-Specific</td>
<td>150 mL for three injections</td>
<td>1800 rpm for 15 min</td>
<td>5 mL</td>
<td></td>
<td>6.5 ± 1.5 million platelets</td>
</tr>
<tr>
<td>Gosens et al.\textsuperscript{3}</td>
<td>knee</td>
<td>Biomet</td>
<td>27 mL</td>
<td>Sodium Citrate</td>
<td></td>
<td>3 mL (22-gauge needle)</td>
<td>\textsuperscript{22-gauge needle}</td>
</tr>
<tr>
<td>Eirale et al.\textsuperscript{37}</td>
<td>MCL</td>
<td>Biomet Recover</td>
<td>27 mL</td>
<td></td>
<td></td>
<td>3 mL (23-gauge needle)</td>
<td></td>
</tr>
<tr>
<td>Yoshida et al.\textsuperscript{38}</td>
<td>MCL</td>
<td>MyCells</td>
<td>20 mL</td>
<td></td>
<td>7 min at 2000g</td>
<td>3 mL LR-PRP</td>
<td>Mean 8.2 x 10\textsuperscript{5} mL</td>
</tr>
<tr>
<td>Lin et al.\textsuperscript{31}</td>
<td>knee</td>
<td>RegenKit</td>
<td>10 mL</td>
<td>None</td>
<td>1500 rpm 8 min</td>
<td>LP-PRP</td>
<td>1.81 +/- 0.34 x baseline</td>
</tr>
<tr>
<td>Di Martino et al.\textsuperscript{35}</td>
<td>knee</td>
<td>Institution-Specific</td>
<td>150 mL</td>
<td>10% Calcium Chloride</td>
<td>1480 rpm for 6 min 3400 rpm for 15 min</td>
<td>4 units of 5 mL LR-PRP</td>
<td>4.6 +/- 1.4 x baseline</td>
</tr>
<tr>
<td>Hamid et al.\textsuperscript{22}</td>
<td>ham-string</td>
<td>GPS III (Biomet)</td>
<td>60 mL</td>
<td></td>
<td></td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td>Rossi et al.\textsuperscript{23}</td>
<td>ham-string</td>
<td>Institution-specific</td>
<td>40 mL</td>
<td>EDTA*</td>
<td>1400g + 3000 rpm for 3 min</td>
<td>3 mL (20 gauge)</td>
<td></td>
</tr>
<tr>
<td>Rowden et al.\textsuperscript{49}</td>
<td>ankle</td>
<td>Magellan</td>
<td>50 mL</td>
<td>Citric Acid</td>
<td></td>
<td>3-4 mL of LR-PRP</td>
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<tr>
<td>Laver et al.\textsuperscript{25}</td>
<td>ankle</td>
<td>Institution-Specific</td>
<td>20 mL</td>
<td>Trisodium citrate &amp; 22.8 mM Calcium Chloride</td>
<td>460 g for 8 min</td>
<td>1.5 mL (21-gauge)</td>
<td>2-3 x baseline</td>
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<tr>
<td>Filardo et al.\textsuperscript{40}</td>
<td>Achilles</td>
<td>Institution-Specific</td>
<td>150 mL</td>
<td>10% Calcium Chloride</td>
<td>1480 rpm 6 min 3400 rpm 15 min</td>
<td>four 5 mL PRP</td>
<td></td>
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<tr>
<td>Boesen et al.\textsuperscript{39}</td>
<td>Achilles</td>
<td>Arthrex</td>
<td>10 mL</td>
<td>No activator</td>
<td>5 min 1500 rpm</td>
<td>4 mL</td>
<td></td>
</tr>
</tbody>
</table>
2.4.3.2 Duration/Frequency

There is heterogeneity among the reviewed studies regarding the timing, frequency, and follow-up of PRP treatment. Several studies use one injection at the start of therapy and follow patients from four, six, eight, twelve weeks. For more chronic conditions, follow-up generally was incremented at 3 and 6 months, and 1 year. Gormeli et al. studied multiple PRP injections for patients with early knee osteoarthritis in comparison to a single injection and a placebo injection. A statistically significant improvement with multiple injections was found. Patients in this treatment group received 2 mL PRP injections at 7-day intervals for a total of three injections. A multiple PRP injection protocol was similarly utilized in other studies for patellar tendinopathy, Achilles tendinopathy, hip osteoarthritis, and high ankle sprain. Because of the acute nature of the MCL injuries we are studying and projected time to recovery, we will be aligning with a study by Rossi et al. who examined PRP for muscle tears with the intervention group protocol involving a single injection and rehabilitation program.

2.4.3.3 Blinding/Randomization

Different blinding and randomization techniques were reviewed. Rossi et al. blinded the evaluators, in this case, physical therapists, by providing all participants with

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Joint</th>
<th>Manufacturer</th>
<th>Volume/mL</th>
<th>Additive</th>
<th>RPM</th>
<th>Volume/mL</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Vos et al.</td>
<td>Achilles</td>
<td>Recover Platelet</td>
<td>45</td>
<td>Citrate</td>
<td>4</td>
<td></td>
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<tr>
<td>Gosens et al.</td>
<td>Elbow</td>
<td>Biomet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peerbooms et al.</td>
<td>Elbow</td>
<td>Biomet</td>
<td>27</td>
<td>8.4% sodium bicarbonate</td>
<td></td>
<td>3 mL (22-gauge)</td>
<td></td>
</tr>
<tr>
<td>Krogh et al.</td>
<td>Elbow</td>
<td>GPS III (Biomet)</td>
<td>27</td>
<td>8.4% sodium bicarbonate</td>
<td>15 min 3200 rpm</td>
<td>3 mL</td>
<td>8 x baseline</td>
</tr>
<tr>
<td>Podesta et al.</td>
<td>UCL</td>
<td>Arterio-cyte</td>
<td>60</td>
<td></td>
<td></td>
<td>5 mL LR-PRP</td>
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</tr>
</tbody>
</table>

*EDTA: Ethylenediaminetetraacetic Acid*
an envelope containing their allocation to one of the two treatment groups and subsequently concealing the results from the physical therapist he or she then worked with. However, subjective VAS scores were obtained from each patient who was not blinded to the treatment they received potentially causing information bias in favor of the PRP injection. In the Dragoo et al. study, participants were assigned to either dry needling or PRP procedure. Blood was drawn from each patient, patients were blindfolded, the area of tendinopathy was penetrated ten times, and PRP was injected for the appropriate patients. Before the injection, 3 mL of 0.25% bupivacaine with 1:100,000 epinephrine was subcutaneously injected. However, the study used 6 mL of PRP, the pressure of which could reasonably have been felt by the patient. Outcomes could have been subject to information bias if the intervention was detected by the patient. Although our study will not compare two different treatments for MCL tears, it will be important to draw blood from all participants to maintain blinding.

Several double blinding protocols were evaluated. The study by Rowden et al. detailed an effective double blinding protocol. Blood was drawn from all patients by an Emergency Department Technician and discarded in the placebo group. A research assistant who was unblinded to the study prepared the injections for the intervention and placebo groups which included lidocaine and bupivacaine in both groups. The injections were then blinded to the investigator and the patient with black tape, a technique utilized by other blinded trials. Importantly, blinding protocols often started with a blood draw from all participants regardless of treatment allocation.

Additionally, the trials investigating PRP for osteoarthritis blinded all patients, drew blood from all patients, and covered the syringe after the respective injections were
prepared. All patients were sent home with instructions to restrict the use of the leg for the first day and to employ rest, ice, compression, and elevation\textsuperscript{33,35,52}. The study by Lin et al. spun every participant's blood regardless of group allocation so every patient spent the same amount of time in the office\textsuperscript{31}. Due to the cost of PRP preparation kits, a reasonable alternative would have been to note the time it takes to prepare a PRP injection and have the control group stay in the office for the same amount of time without centrifuging their blood.

2.4.3.4 Control Groups/Standard of Care

Physical therapy regimens are considered the standard of care in the conservative treatment of MCL injuries. There is no single physical therapy program that has been shown to be more beneficial, but studies generally emphasize early range of motion followed by quadriceps and hamstring strengthening\textsuperscript{63}. The study used to calculate our sample size detailed a rehabilitation program that is commonly used in MCL injury recovery\textsuperscript{64}. They included quadricep isometric contraction, standing and squat-and-stand-up movements, and thigh adductor and abductor muscle exercises\textsuperscript{64}. This study was the only empirical trial found that utilized a control physical therapy group so the examination of studies that outline the usual practice for MCL physical therapy as detailed in section 1.1.5 will be used to define our study protocol.

However, the studies investigating PRP use differing comparison groups. Another one of the studies used in our sample size calculation examined the effect of PRP and patellar tendinopathy in comparison to focused shock waves\textsuperscript{4}. Although different populations from our proposed study, some randomized controlled trials used a control physiotherapy group\textsuperscript{23,25,53}. When blinding was involved, standard therapy and a placebo
injection was used. In the setting of PRP for arthritic conditions, PRP injections were often compared to hyaluronic acid or glucocorticoid injections. However, some prospective investigations offering platelet-rich plasma do not include a comparison group. The study by Boesen et al. investigating PRP for Achilles tendinopathy used an isotonic saline injection for the control group. During the injection, the needle was inserted slightly away from the tendon just under the skin so as not to affect any tissue and then held still to resemble the duration of a PRP injection. Other studies simply inserted the needle and held it in place for a similar duration to a full PRP injection, although it was noted in one study that patients might be able to discern whether they were receiving an injection, which would threaten the patient blinding. The double-blind protocols for osteoarthritis often used a placebo injection as a third comparison group to PRP versus HA injections. After a review of the above studies, we will be utilizing a placebo injection of isotonic saline in combination with standard physical therapy for our control group.

2.4.4 Primary and Secondary Outcome Measures

Mean change in Visual Analog Scale (VAS) scores, a subjective measure of pain, will be the primary outcome for our study. This scale was chosen for the frequency of its use as a primary or secondary outcome in the reviewed literature and the ability to calculate a feasible sample size for our study. The scale is a 10 cm line where the left endpoint is designated “no pain” and the right endpoint is “worst pain imaginable” (see Figure 1). Traditionally, the patient marks the point along the scale that he or she feels is most reflective of his or her current pain state. It is designed to gauge the intensity of pain a patient is feeling at the time of completion. Advantages of the scale include
feasibility since the time to respond usually takes less than one minute\textsuperscript{66}. The scale also requires little training to administer. Additionally, a recent study examining orthopaedic sports medicine patients found no significance difference between VAS scores completed on paper, on a laptop, or on a mobile device\textsuperscript{67}. Therefore, our study will use Adaptive Visual Analog Scales software to evaluate pain scores as a continuous variable\textsuperscript{68}. In order to quantify the effect of PRP intervention, the VAS score will be taken at baseline, at two weeks, at four weeks, and at six weeks and the net change from baseline will be calculated, similar to the calculations outlined by Dragoo et al.\textsuperscript{5}.

Return to play was the primary outcome for the case studies on the use of PRP in MCL tears\textsuperscript{36-38}. Similarly, studies investigating PRP for acute muscle tears\textsuperscript{23} and hamstring tendon injuries\textsuperscript{48,53} use return to play as the primary outcome. As there is no gold standard criteria for return to play, some studies defined individual criteria\textsuperscript{53}, while others used full return to practice and games or matches as the definition of return to play\textsuperscript{23,53}. For the purpose of our study, we were able to make a more robust assessment of the necessary sample size to detect a significant result using a pain scale as our primary outcome. Additionally, we chose a pain scale over return to play in order to broaden the application of PRP for MCL tears beyond athletes. However, enhancement of the healing process becomes especially important in athletics, with the stakes heightening with each higher level of play. Therefore, return to activity will be a secondary outcome. Our study will define return to activity as the ability to participate in the participants baseline activities before the time of injury with no pain.

Our other secondary outcomes will be the International Knee Documentation Committee (IKDC) evaluation form and Lysholm scores. In the evaluation of grade III
MCL tears in the setting of concurrent ACL injury, IKDC and Lysholm were primary outcomes\textsuperscript{69}. These scales are commonly used patient reported outcome measures in clinical studies of knee conditions. The IKDC evaluation was created to standardize various scales that were being used by breaking down knee pain into symptoms, sports activities, and function\textsuperscript{70}. We will be using the 2000 International Knee Documentation Committee Subjective Knee Evaluation form\textsuperscript{71} (see Appendix A). The second scale will be the Lysholm score which is based on the following symptoms: pain, swelling, limp, use of cane or crutches, locking sensation in the knee, giving way sensation from the knee, pain with climbing stairs and with squatting\textsuperscript{72}. The original knee form was documented by Lysholm et al. (see Appendix B)\textsuperscript{73}.

2.4.5 Sample Size and Statistical Analysis

The literature review did not yield any randomized controlled trials examining the effect of platelet-rich plasma on recovery from medial collateral ligament tear of any grade. Therefore, our sample size calculation includes data from three studies. We calculated relative effect found and extrapolated this information to estimate the effect size for our intervention and study population. Ding et al. conducted a study evaluating acupuncture as an augment to physical therapy for MCL tears\textsuperscript{64}. The study measured the effect of the intervention with the VAS pain scale at baseline and four weeks. At baseline, the mean VAS score was $5.17 \pm 1.56$\textsuperscript{64}. At 4 weeks, the mean score was $2.57 \pm 1.0$\textsuperscript{64}. This study was chosen to represent the mean expected improvement in VAS of our population for the standard of care of MCL tears.

The study populations of the two remaining studies were patients with patellar tendinopathy. Vetrano et al. measured the effect of PRP on patella tendinopathy in
comparison to focused shock wave treatment. At baseline, the mean VAS score for the PRP group was $6.6 \pm 1.8$. At 6 months, the mean score was $2.4 \pm 1.9$. The relative effect and standard deviation were -4.2 and 1.85 respectively. The decision was made not to compare this effect to the study’s comparison group who underwent extracorporeal shockwave therapy (ESWT) because it did not represent a true control group. Zwerver et al. examined ESWT therapy for patellar tendinopathy in comparison to a placebo group.

The majority review of the previous studies that included sample size calculations utilized an alpha of 0.05 and power of 80%. Therefore, these parameters were used to calculate our sample size, details of which are located in the Chapter 3 and in Appendix C.

2.5 CONCLUSION

The literature review supports the use of PRP in a variety of orthopaedic conditions and highlights the need for a randomized controlled trial investigating the effect of PRP augmentation for treatment of MCL injury. To date, there is no consensus on the effect of PRP on MCL tears although case studies have indicated positive results. A double-blind placebo-controlled randomized trial will most effectively examine the proposed benefit of PRP on higher grade MCL tears. Recruitment of patients with grade II and III MCL tears will allow for a clear treatment effect as higher grade tears are more likely to require more intensive treatment for recovery. Comparison of VAS scores along with International Knee Documentation Committee (IKDC) forms, Lysholm scores, and return to activity will effectively quantify the effect of PRP injections in this patient population.
2.6 REFERENCES


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70. 2000 IKDC SUBJECTIVE KNEE EVALUATION FORM.
72. Lysholm Knee Scoring Scale.
CHAPTER 3: STUDY METHODS

3.1 STUDY DESIGN

We propose a randomized, double-blind, placebo-controlled trial investigating the effect of platelet-rich plasma on recovery from acute isolated grade II and III medial collateral ligament tears in comparison to the standard of care physical therapy protocol. Participants will be assigned to either Group 1, the intervention group, or Group 2, the control group by a computer-generated randomization. Group 1 will receive an injection of platelet-rich plasma and a physical therapy regimen for MCL tears. Group 2 will receive a placebo injection of normal saline in addition to the current standard of care physical therapy for MCL tears.

3.2 STUDY POPULATION AND SAMPLING

The study population will include adults aged 18–45 years old with grade II or III MCL tears who are evaluated at Yale Orthopaedics and Rehabilitation clinical sites. MCL tears can be diagnosed clinically or by magnetic resonance imaging (MRI). All participants will be graded clinically and confirmed with MRI. Eligible patients will be recruited using convenience sampling from Yale Orthopaedics and Rehabilitation outpatient clinic for one year and six months. Any patient who meets inclusion and exclusion criteria will be eligible to participate. During the initial appointment and clinical confirmation of a grade II or III MCL tear, patients will be introduced to the study. MRI confirmation of the MCL tear will be conducted after the participants are committed to the study. If a patient who qualifies for the study has already obtained an MRI and brings the disc of images and the associated report during the initial consult, this will satisfy the requirement for MRI confirmation.
3.2.1 Inclusion Criteria

Inclusion criteria will include acute grade II or III isolated medial collateral ligament tears. Participants aged 18-45 are eligible to participate. An acute tear will be defined as injury occurring less than fourteen days prior to treatment. All study participants will confirm an isolated MCL tear diagnosis with an MRI and baseline characteristics and baseline Visual Analog Scale (VAS), International Knee Documentation Committee (IKDC), and Lysholm scores will be collected at the participant’s MRI follow-up appointment. Before this follow-up appointment, if patients meet the inclusion criteria, he or she will be contacted and instructed to obtain the following screening labs: CBC, ESR and CRP. Bloodwork within the previous one month will also be accepted.

3.2.2 Exclusion Criteria

Exclusion criteria will include grade III MCL tears with associated avulsion at the tibial insertion, medial instability of > 5 mm, multiligamentous injuries including the ACL, PCL or posterolateral corner injury, previous ipsilateral knee surgery. Mild MCL tears (grade I), chronic MCL tears, and tears previously treated with physical therapy will also be excluded. Further, we will exclude pregnancy, history of bleeding disorder, Hemoglobin < 11 g/dL, Hematocrit < 33%, platelet count outside of the normal range from 150-400 x 100/uL, participation in a workers’ compensation program, local corticosteroid injection within 6 weeks to the ipsilateral knee, current anticoagulation or antiplatelet therapy, history of thrombocytopenia.
3.3 SUBJECT PROTECTION AND CONFIDENTIALITY

We will attain Yale Institutional Review Board (IRB) approval for our study prior to recruitment. We will be adhering to the 100 IRB Protocol for review of human subject research protocols or FDA-regulated activities involving human participants. The consent for our study will explain the potential risks of participating in a research protocol and, more specifically, disclose the potential risks of platelet-rich plasma intra-articular injection. Clear explanation of measures to maintain confidentiality and privacy practices will be disclosed. A written, informed consent form will be completed by all study participants. A sample consent form is can be found in the appendix (Appendix D).

Because of the proposed blinding of our study, study personnel will complete Health Insurance Portability and Accountability Act (HIPAA) training. Participant data will be kept confidential within university provided password-protected encrypted servers.

3.4 RECRUITMENT

Recruitment will primarily take place at Yale Orthopaedics & Rehabilitation outpatient clinical sites in New Haven, Guilford, Stamford, and Milford, Connecticut. Patients aged 18-45 who present to Yale Orthopaedics & Rehabilitation will provided with information about the study if they meet the inclusion criteria. Upon MRI confirmation of an isolated grade II or III MCL tear, the study team will meet in-person with the participants who are interested in the study at their follow up visit. In the event of a patient who has obtained MRI confirmation of an isolated grade II or III MCL tear prior to the initial appointment at Yale Orthopaedics & Rehabilitation, the patient will be eligible for participation in the study.
3.5 STUDY VARIABLES AND MEASURES

3.5.1 Independent Variables

Baseline variables will include age, gender, height, weight, baseline measures (VAS, IKDC, Lysholm), duration of symptoms, affected knee, level of sports activity (elite athletes vs recreational athletes) and primary sport played if applicable, and exercise level/cardiac fitness. Cardiac fitness will be defined as adults who exercise at medium intensity aerobic activity (biking, walking, jogging/running) 3-5 times a week for 20-60 minutes. It will be evaluated as a dichotomous variable by meeting this criterion or not.

The intervention will be a single platelet-rich plasma injection. The PEAK Platelet-rich Plasma System by DePuy Synthes Mitek Sports Medicine\(^1\) will be the commercially available PRP kit used in this study. For each patient, the first step will be a 30 mL peripheral blood draw with an 18-gauge needle by a nurse. To maintain blinding, the research assistant will be present at all injection visits in order to complete the computer-generated randomization for each participant. The injection will be prepared outside of the patient’s room by a nurse who will be given the patients group allocation. The preparation of the injectate will begin with the addition of 3 mL of Anticoagulant Citrate Dextrose A Solution (ACD-A) to the 30 mL syringe. The mixture of blood and ACD-A will then be placed in the disposable unit provided by Depuy to centrifuge the blood for one minute. Following the instructions for device use, the nurse will extract the layer of PRP into a syringe, discarding the layers of red blood cells and platelet poor plasma, resulting in 3 mL of PRP for injection. The resulting injection will contain 6.8 ± 1.1 times the normal concentration of platelets\(^1\). Additionally, white blood cell
concentration will be 5 times the normal concentration\(^1\). No activator (such as calcium chloride) will be added. The time taken to prepare the injection will be noted. A piece of black tape will then be placed around the syringe to conceal the contents and ensure blinding of the primary investigator and patient.

The point of maximal tenderness on the femoral side of the MCL will be marked. The surrounding skin will be sterilized with 2\% chlorhexidine. Using aseptic technique, the PRP will slowly be injected into the ligament with an ultrasound guidance using a 22-gauge 1.5-inch needle. The knee will then be bandaged and the participant will be instructed to be weight-bearing as tolerated, using crutches as necessary, with progression to light aerobic activity as tolerated after one week. At one week, participants will also start physical therapy.

The intervention group will be compared to a placebo injection group as the control group. To maintain double blinding, a blood sample will be taken from all patients in the control group by a nurse and removed from the patient’s room. A 3 mL injection of 0.9\% normal saline will be prepared. A piece of black tape will be placed around the syringe and the nurse will wait to give the primary investigator the injection until a time comparable to the average time noted to obtain the treatment group injection.

Just as in the intervention group, the point of tenderness on the femoral side of the MCL will be marked. The surrounding skin will similarly be sterilized with a 2\% chlorhexidine. Using aseptic technique, the injection will occur under ultrasound guidance using a 22-gauge needle. Patients will be identically bandaged to the PRP group with the same weight-bearing instructions. The physical therapy program will also begin one week after the placebo injection.
All participants, in both study arms, will undergo physical therapy that is the standard of care for MCL rehabilitation. Standard physical therapy for MCL tears include quadriceps and leg muscle strengthening and early range of motion protocols followed by a progressive return to functional and sport-specific movements. The goal of physical therapy will be full pain-free range of motion and at least 90% strength of the hamstring and quadriceps as the contralateral knee. The duration of therapy will be 4-6 weeks. See Appendix F for a sample physical therapy program. Patients may also be given a hinged knee brace on a case by case basis as determined by the treating provider and use or not of a brace will be included in the data analysis. Adherence to physical therapy will be monitored through weekly physical therapy progress reports. Patients will also be asked at their two and six-week follow up about their satisfaction with physical therapy and whether they have missed any sessions. If non-adherence to the protocol is found, the participant will be reached out to by phone to encourage full participation.

3.5.2 Dependent Variables

The primary outcome will be Visual Analog Scale scores will be conducted at baseline, at two weeks, at four weeks, and at six weeks. After the appointment where the injection was performed, patients will be scheduled for follow-up appointments at two and six weeks. For patients who prefer electronic surveys, a Qualtrics survey with the VAS instrument will be sent out at the appropriate intervals by email to each study participant (see Appendix H for full details). Participants will also have the opportunity to complete the surveys in the office with the research assistant if preferable, who will then enter the study participant’s answers to the survey online. If the study participant misses a follow-up appointment or does not complete an online study, reminder emails will be sent
to prompt completion of the scales as close to the desired time intervals as possible. If not completed within three days of the follow-up email, a call will be placed to the study participant. Importantly, patients will be instructed not to take any non-steroidal anti-inflammatory medications on the day of VAS data collection. Mean change in VAS score from baseline will be calculated at two, four, and six weeks.

The secondary outcomes are return to baseline activity or sport and mean change in IKDC and Lysholm scores. Scores will be obtained at baseline, at two, at four weeks, and at six weeks. On the day of completion of the scores, patients will be instructed not to take any NSAIDs or acetaminophen so as not to minimize pain that the patient would normally be feeling at the time of completion of the forms. Return to baseline activity or sport will be discerned with a Qualtrics survey at four and eight weeks asking whether the patient has returned to baseline activity, and, if so, on what date (see Appendix I). Return to activity will be assessed as a time to event variable.

3.5.3 Blinding of Intervention

At the time of injection, a computer randomization process will allocate participants into either the placebo or intervention arm, and the research assistant will place the assignment into a white envelope without seeing the contents. Injections of PRP for the intervention group and normal saline for the placebo group will be prepared in the Yale Orthopaedics & Rehabilitation clinic by an unblinded nurse who will receive the envelope from the research assistant. The injections will be blinded to the investigator who will perform the injection by the application of black tape to conceal the syringe contents. Similarly, the patient will be blinded. Additionally, the radiologist who will be reading the MRI results at the initial time of injury will be blinded to the study
intervention and the physical therapist that the participant works with after the procedure will not be aware of the treatment allocation.

3.5.4 Assignment of Intervention

Computer-generated randomization will assign patients in a 1:1 ratio to either the PRP or placebo group. The allocation will be concealed in an envelope by the research assistant until the nurse opens the envelope to prepare the injection. All other study personnel will be blinded to treatment allocation. Patients will similarly be blinded to treatment allocation and will have agreed to participate in the study regardless of their assigned group.

3.5.5 Adherence

Due to the single injection protocol we will be employing, it is critical that participants attend their clinic appointment where the injection will be performed. For patients who qualify for the study based on clinical diagnosis and who have expressed interest in the study, baseline pain scale scores, VAS scores, IKDC form and Lysholm score will be completed at this appointment, prior to MRI confirmation. After MRI confirmation of an isolated grade II or III MCL tear, patients will be asked to obtain basic labs (CBC, ESR, CRP) and to schedule a follow-up appointment to discuss results, eligibility for our study, and scheduling of the injection. Patients will be reminded of their appointment one day prior to the scheduled date.

Patients will have the option to undergo the injection the same day as their follow-up appointment, provided they have completed all the required paperwork ahead of the appointment. Patients who qualify for the study and are interested in an injection during their MRI follow-up appointment will be instructed to come to the office early for
paperwork review with the research assistant. Otherwise, a confirmatory phone call will also be made to participants the day before the appointment for the injection. After the injection, patients will be instructed have a two week and six-week follow-up appointment. To ensure completion of the pain scales as close to the designated time intervals of two, four, and six weeks, a digital version of the pain scales will be sent out to participants to obtain the pain scores. Participants will also have the opportunity to fill out the forms with the research assistant during a follow-up appointment. If a follow-up appointment is missed, the digital pain scales will be sent out and the appointment be rescheduled.

Compliance with the physical therapy regimen will be essential to the validity of our study. To improve generalizability of our study, patients will choose a physical therapy location that is most convenient for them. We will be requesting physical therapy progress reports on a weekly basis for study participants. These reports will be signed by the primary provider overseeing the study. Patients who miss more than one physical therapy session per week will receive follow-up calls.

3.5.6 Monitoring of Adverse Events

It is estimated that 1 in 70,000 intra-articular injections result in septic arthritis. Studies have emphasized the importance of aseptic technique which will be a priority in our study. After the injection, patients will be called to monitor adverse events. Adverse events in PRP injections have been shown to be minor, but reports of increased pain and swelling in the first week have occurred. Therefore, we will be documenting the number of participants with increase pain and swelling within the first week and participants with increased pain lasting longer than a week. Patients will be instructed to call the principal
investigator with any concerns of prolonged increased pain or other concerns about the injection. Additionally, a recent metanalysis investigating normal saline as a placebo intervention for knee osteoarthritis found that adverse events was only reported in one study with two patients; the remaining thirteen studies reported that the injection was well-tolerated\textsuperscript{4}.

3.6 DATA COLLECTION

Patients with a clinically diagnosed grade II or III MCL tear who are interested in participating in the study will complete a demographic and screening survey at baseline and baseline characteristic data will be compiled (see Appendix E). Baseline characteristics included in the survey will include age, gender, height, weight, affected knee, duration of symptoms, sports activity (elite athletes vs recreational athletes) and sport involved if applicable, and exercise level/cardiac fitness. Patients who meet inclusion criteria will then complete baseline pain scores including the VAS scale, IKDC form and Lysholm scores.

Following this data collection, patients will then obtain MRI confirmation of a grade II or III isolated MCL tear. For those who continue to be eligible for the study after MRI, baseline CBC, ESR and CRP testing will be obtained. Patients with abnormal labs will be treated appropriately and can be reconsidered for participation in the study with findings of normal lab values on recheck of lab work. Patients will be scheduled for two- and six-week follow-up appointments where the three pain scales and forms will be completed, providers will monitor of adherence to physical therapy regimen, and note any adverse events.
The other secondary outcome is return to activity. Participants will complete a survey at four weeks and eight weeks to assess whether or not they feel they have returned to baseline activity, or when applicable, returned to sport. This is a time to event variable.

3.7 SAMPLE SIZE CALCULATIONS

The sample size calculation was calculated from three studies with the primary outcome of mean change on the VAS scores. VAS is a continuous variable quantified on a scale from 1-10. The sample size calculation was first calculated using the Power and Precision software. To ensure the accuracy of the calculator, the G*Power 2 calculator was used. The calculation was made based on the assumption that a continuous, normally distributed outcome would be compared between the augmented PRP group and placebo treatment group using a Student’s t-test.

The mean of the population was extrapolated from the study by Ding et al.\textsuperscript{5} who found a mean change in VAS scores after a course of physical therapy, the standard of treatment for MCL tears, of $-2.6 \pm 1.31$. To relate the relative effects from the Vetrano\textsuperscript{6} and Zwerver\textsuperscript{7} studies, the overall mean change and standard deviation were calculated. The overall relative effect on VAS was calculated to be 3.6; the calculated standard deviation was 2.296. Finally, the relative effect of PRP on patellar tendinopathy was compared to the relative effect of physical therapy for MCL tears as an estimation of the effect that PRP would have on MCL tears. For a two-sided test with $\alpha = 0.05$ and power of 80\%, 56 patients in each group of the study will need to be recruited. In order to account for a 15\% attrition rate, 8 additional patients in each group will be added. With
these additional participants, the final sample size needed for our study is 128 patients with 64 in each group (See Appendix C for the full sample size calculation).

3.8 ANALYSIS

Data will be analyzed by the intention-to-treat principle by including all patients who will be randomized. Continuous baseline variables will be compared between the PRP group and the placebo group using a Student’s t-test. This will include age, gender, height, weight, and duration of symptoms. Dichotomous and categorical baseline variables will be compared using Chi-Squared test. This will include affected knee, level of sports activity, cardiac fitness, and primary sport if applicable. A p value of < 0.05 will indicate a significant result finding in a two-tailed statistical test.

The primary outcome mean change in VAS scores from baseline is a continuous variable and will be compared between the PRP and placebo groups using a Student’s t-test. To compare within the PRP and placebo groups, a paired t-test will be used. If the data is not normally distributed a Mann Whitney U test will be used to compare between the PRP and placebo groups and a Wilcoxon Signed-Rank test will be used to compare within the PRP and placebo groups. The secondary outcomes are return to activity, the IKDC questionnaire, and Lysholm scores. Mean change in IKDC and Lysholm scores are both continuous variables and will be compared between groups using a Student’s t-test and within groups using an unpaired t-test. Return to activity will be a time to event variable and will be compared using a Kaplan-Meier analysis. Assessment of the relationship between change in VAS scores and other potential confounding variables will be completed using multiple linear regression. These will include age, gender,
height, weight, sports activity (elite athletes vs nonelite athletes), sport involved if applicable, and exercise level/cardiac fitness, and use or not of a brace.

3.9 TIMELINE AND RESOURCES

The proposed study period will be two years including recruitment, protocol completion, and patient follow-up beginning January 1, 2021. The first 16 months of the study will be utilized for recruitment of the 128 patients with grade II and III MCL tears aged 18-45. Eligible participants will undergo randomization for PRP therapy and will receive one injection at the start of treatment on a rolling basis. The course of physical therapy will last four to six weeks followed by monthly follow-up to assess the status of full return to activity. See Figure 2 for a diagram of the proposed study timeline. The personnel requirement for the study will be a principal investigator and co-investigator for overseeing the study progress, and additional physicians, nurse practitioners, and physician assistants who will recruit patients seen in his or her clinics. A nurse will be needed for the preparation of the PRP injection, and a radiologist will be needed to interpret the MRI images. A research assistant will be needed for data entry and randomization, and a data analyst will be needed.

3.10 REFERENCES

CHAPTER 4: CONCLUSIONS

4.1 ADVANTAGES AND DISADVANTAGES

One of the biggest strengths of our study is the study design of a randomized controlled trial. Conservative treatment of the MCL is a generally accepted practice under the correct clinical circumstances, however, recent clinical trials quantifying the effect of a treatment protocol is lacking. Our study not only will allow us to examine the effect of PRP on healing of the MCL but will provide a control comparison group using the current standard of care rehabilitation protocol. Another strength of our study is that both the intervention group and the control group will be receiving standard of care physical therapy which will allow us to determine the additional effect that PRP will have on recovery from MCL injury.

Additional strengths of our study include the MRI confirmation of the grade of MCL tear, the restriction to acute MCL tears, and the blinding protocol. MRI confirmation of a grade II or III isolated MCL tear will minimize the risk for residual laxity and instability after our intervention and treatment protocol by appropriately excluding patients likely to benefit from definitive surgical treatment. Restriction to acute MCL tears will allow for the most accurate estimation of the effects of PRP therapy augmentation. Within the tendinopathy subset of the literature, there were more consistently significant results in acute injuries like patella tendinopathy naïve to treatment versus more chronic pathology such as Achilles tendinitis.

Our study protocol is another strength. After reviewing the literature, the extreme variation in protocol and blinding leads to questions about the generalizability of previous studies investigating PRP injections. Our study will build on the previous literature by
effectively blinding all participants and appropriate study personnel in an effort to eliminate biased data collection. The pain scales should therefore not be influenced by the anticipated effect that PRP will have on his or her injury, nor will the physical exams completed by the providers be biased toward a more benign exam in the intervention group during follow-up. The secondary outcome pain scales, IKDC and Lysholm, are another strength as it will allow for comparison to previous studies using these scales. Similarly, our study includes an extensive list of baseline characteristics that will all be analyzed as potential confounders, thus increasing the likelihood that any positive findings in our study will be attributable to the effects of PRP therapy.

A study limitation includes the rarity of an isolated grade III MCL tear due to frequent concomitant injury with the severity of this injury. This led us to the decision to include grade II MCL tears which encompass the largest range in severity of tear. The heterogeneity of grade II tears might lead to recruitment of a mild tear that still qualifies as grade II versus a very nearly complete tear of the MCL. Depending on the relative severity of grade II tears represented in our study sample, our results could be under or overestimated. However, grade II and III tears often have similarities that can result in a longer recovery, which is the target of PRP therapy. Another limitation is the relatively short follow up period. Although most MCL tears fully resolve by eight weeks, maintenance of pain free symptoms is not something our study can assess. We are therefore unable to include information about refractory cases of MCL injury to treatment, both of our intervention and the standard of care, although this is not the primary focus of our study. A final limitation includes the cost of PRP as it is generally not covered by insurance.
4.2 CLINICAL SIGNIFICANCE

The medial collateral ligament is the most commonly injured knee ligament\textsuperscript{1-6}. For grade II and III MCL tears, the standard of care involves functional rehabilitation and physical therapy but results in a loss of injury ranging three to eight weeks\textsuperscript{7-10}. PRP has the potential to augment recovery of MCL injuries and reduce the burden of injury. By increasing the concentration of healing components that are naturally found in whole blood, patients may be able to return to activity sooner and become pain-free faster. Additionally, lower pain scores might allow patients to proceed more rapidly through a physical therapy regimen. Successful conservative treatment of MCL injuries would preclude the need for surgical intervention which is often favored. This study will provide insight into whether PRP is a viable option for adjunct treatment more severe grades of MCL tears and open the door for additional investigations.

Future direction for studies to build off of our results include studying the application of this treatment in the elite athlete population if a significant effect were to be found. Although our study population is not limited to elite athletes, decreasing the time lost to injury is highly of particular interest to the athletic community. Effective conservative treatment of acute injuries in athletes at collegiate and professional level for example would help to decrease the stress and pressure to recover quickly that may be felt after injury. If PRP treatment is not found to be significant in our study population, further investigation into alternative conservative treatment is warranted. However, PRP therapy is a promising treatment for acute pathologies as an augmentation of the body’s natural healing response and has the potential to be beneficial in a variety of settings including injuries to the medial collateral ligament.
4.3 REFERENCES


APPENDICES

Figure 2: Study Design

<table>
<thead>
<tr>
<th>Enrollment: 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MRI + Pain Scales + Lab work</td>
</tr>
</tbody>
</table>

Allocation

PRP injection + Physical Therapy

Placebo Injection + Physical Therapy

<table>
<thead>
<tr>
<th>Week 2 Follow-up appointment and completion of VAS, IKDC, Lysholm scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 completion of VAS, IKDC, Lysholm, return to activity (and on what date)</td>
</tr>
<tr>
<td>Week 6 Follow-up appointment and completion of VAS, IKDC, Lysholm scores</td>
</tr>
<tr>
<td>Week 8 Phone call follow-up yes/no return to activity (and on what date)</td>
</tr>
</tbody>
</table>
**Appendix A: International Knee Documentation Committee Evaluation Form**

**2000 IKDC SUBJECTIVE KNEE EVALUATION FORM**

<table>
<thead>
<tr>
<th>Name:</th>
<th></th>
<th></th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td></td>
<td>Last</td>
<td></td>
</tr>
</tbody>
</table>

**Physician:**

<table>
<thead>
<tr>
<th>Date of Injury:</th>
</tr>
</thead>
</table>

**SYMPTOMS**: *Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.*

1. **What is the highest level of activity that you can perform without significant knee pain?**
   - Very strenuous activities like jumping or pivoting as in basketball or soccer
   - Strenuous activities like heavy physical work, skiing or tennis
   - Moderate activities like moderate physical work, running or jogging
   - Light activities like walking, housework or yard work
   - Unable to perform any of the above activities due to knee pain

2. **During the past 4 weeks, or since your injury, how often have you had pain?**
   
<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Constant</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

3. **If you have pain, how severe is it?**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Worst pain imaginable</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

4. **During the past 4 weeks, or since your injury, how stiff or swollen was your knee?**
   - Not at all
   - Mildly
   - Moderately
   - Very
   - Extremely

5. **What is the highest level of activity you can perform without significant swelling in your knee?**
   - Very strenuous activities like jumping or pivoting as in basketball or soccer
   - Strenuous activities like heavy physical work, skiing or tennis
   - Moderate activities like moderate physical work, running or jogging
   - Light activities like walking, housework or yard work
   - Unable to perform any of the above activities due to knee swelling

6. **During the past 4 weeks, or since your injury, did your knee lock or catch?**
   - Yes
   - No

7. **What is the highest level of activity you can perform without significant giving way in your knee?**
   - Very strenuous activities like jumping or pivoting as in basketball or soccer
   - Strenuous activities like heavy physical work, skiing or tennis
   - Moderate activities like moderate physical work, running or jogging
   - Light activities like walking, housework or yard work
   - Unable to perform any of the above activities due to giving way of the knee

https://www.sportsmed.org/aossmimis/Staging/Research/IKDC_Forms.aspx
SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?
   - Very strenuous activities like jumping or pivoting as in basketball or soccer
   - Strenuous activities like heavy physical work, skiing or tennis
   - Moderate activities like moderate physical work, running or jogging
   - Light activities like walking, housework or yard work
   - Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not difficult at all</th>
<th>Minimally difficult</th>
<th>Moderately Difficult</th>
<th>Extremely difficult</th>
<th>Unable to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Go up stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Go down stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Kneel on the front of your knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Squat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Sit with your knee bent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Rise from a chair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Run straight ahead</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Jump and land on your involved leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Stop and start quickly</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

<table>
<thead>
<tr>
<th>Rating</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No limitation in daily activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couldn't perform daily activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CURRENT FUNCTION OF YOUR KNEE:

<table>
<thead>
<tr>
<th>Rating</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No limitation in daily activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot perform daily activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IKDC Score
Appendix B: Lysholm Knee Scoring Scale

**LYSHOLM KNEE SCORING SCALE**

Instructions: Below are common complaints which people frequently have with their knee problems. Please check the statement which best describes your condition.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LIMP:</td>
<td>PAIN:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have no limp when I walk.</td>
<td>I have no pain in my knee.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have a slight or periodical limp when I walk.</td>
<td>I have intermittent or slight pain in my knee during vigorous activities.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have a severe and constant limp when I walk.</td>
<td>I have marked pain in my knee during vigorous activities.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>USING CANE OR CRUTCHES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not use a cane or crutches.</td>
<td>I have marked pain in my knee during or after walking more than 1 mile.</td>
</tr>
<tr>
<td>I use a cane or crutches with some weight-bearing.</td>
<td>I have marked pain in my knee during or after walking less than 1 mile.</td>
</tr>
<tr>
<td>Putting weight on my hurt leg is impossible.</td>
<td>I have constant pain in my knee.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOCKING SENSATION IN THE KNEE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no locking and no catching sensations in my knee.</td>
<td>I have no swelling in my knee.</td>
</tr>
<tr>
<td>I have catching sensation but no locking sensation in my knee.</td>
<td>I have swelling in my knee only after vigorous activities.</td>
</tr>
<tr>
<td>My knee locks occasionally.</td>
<td>I have swelling in my knee after ordinary activities.</td>
</tr>
<tr>
<td>My knee locks frequently.</td>
<td>I have swelling constantly in my knee.</td>
</tr>
<tr>
<td>My knee feels locked at this moment.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GIVING WAY SENSATION FROM THE KNEE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>My knee never gives way.</td>
<td>I have no problems climbing stairs.</td>
</tr>
<tr>
<td>My knee rarely gives way, only during athletics or other vigorous activities.</td>
<td>I have slight problems climbing stairs.</td>
</tr>
<tr>
<td>My knee frequently gives way during athletics or other vigorous activities, in turn I am unable to participate in these activities.</td>
<td>I can climb stairs only one at a time.</td>
</tr>
<tr>
<td>My knee occasionally gives way during daily activities.</td>
<td>Climbing stairs is impossible for me.</td>
</tr>
<tr>
<td>My knee often gives way during daily activities.</td>
<td></td>
</tr>
<tr>
<td>My knee gives way every step I take.</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL** /100

### Appendix C: Sample Size Calculation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up Measure</th>
<th>Relative Effect</th>
<th>Standard Deviation</th>
<th>Overall 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (PRP for Patellar Tendinopathy)</td>
<td>6.6 ± 1.8</td>
<td>6 months: 2.4 ± 1.9</td>
<td>6.6 − 2.4 = 4.2</td>
<td>(\sqrt{\frac{1.8^2 + 1.9^2}{2}} = 1.85)</td>
<td>4.2 ± 1.85</td>
</tr>
<tr>
<td>Group 2 (PT control group for EWST intervention)</td>
<td>4.6 ± 2.3</td>
<td>22 weeks: 4.0 ± 3.0</td>
<td>4.6 − 4.0 = 0.6</td>
<td>(\sqrt{\frac{2.3^2 + 3.0^2}{2}} = 2.67)</td>
<td>.6 ± 2.67</td>
</tr>
<tr>
<td>Mean Change Between Group 1 and 2</td>
<td>Overall Relative Effect: 4.2 − .6 = 3.6</td>
<td>(\sqrt{\frac{1.85^2 + 2.67^2}{2}} = 2.296)</td>
<td>3.6 ± 2.296</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCL Treatment Standard of Care</td>
<td>5.17 ± 1.56</td>
<td>4 weeks: 2.57 ± 1.0</td>
<td>5.17 ± 2.57 = 2.6</td>
<td>(\sqrt{\frac{1.56^2 + 1.0^2}{2}} = 1.31)</td>
<td>2.6 ± 1.31</td>
</tr>
</tbody>
</table>

Sample Size Summary:

- **Tails**: Two
- **Type I error rate**, \(\alpha = 0.05\)
- **Power**, \(1 − \beta = 0.80\)
- **Confidence interval**: 0.3 – 1.7
- **Total calculated sample size**: 112

Size per group \((n)\): 56

Assuming 15% attrition rate, 8 additional participants will be added to each arm:

- **Final sample size**: 128
- **Size per group \((n)\)**: 64
Appendix D: Adult Consent Form for Participation in a Research Project

Adult Consent for Participation in a Research Project
200 FR 9 (2017-2)

Title: Platelet-Rich Plasma for the Treatment of Acute Grade II and III Medial Collateral Ligament Tears in Patients Aged 18-45

Principal Investigator: Samantha Smith MD
Co-Investigator: Maddie Kratz

Introduction

You are being asked to join a research study. The following information will explain the purpose of the study, what you will be asked to do, and the potential risks and benefits. You should ask questions before deciding whether you wish to participate, or at any time during the course of the study.

Purpose

The purpose of this study is to investigate the potential benefit of Platelet-Rich Plasma (PRP) in addition to the standard of care physical therapy regimen for Medial Collateral Ligament (MCL) tears. You are being asked to participate because you have been identified as someone who meets the inclusion criteria for the study based on the severity of your MCL tear as diagnosed clinically and/or confirmed with Magnetic Resonance Imaging (MRI).

Procedures

If you choose to participate in the study, you will be asked to obtain basic blood tests, an MRI of your knee, and to schedule a follow-up appointment to discuss the results of your MRI, complete three questionnaires. You will then be randomized to either the treatment group or the control group. To maintain the integrity of the research protocol, you will not be told whether you have been assigned to the treatment group or the control group. The treatment group will receive an injection of platelet-rich plasma into the MCL tear. This will be prepared by first obtaining some of your blood and spinning it in a machine (called a centrifugation process) that will separate out the PRP from the whole blood specimen. Regardless of whether you are randomized to the treatment group or the control group, you will have your blood drawn. The control group will not receive an injection of PRP but will instead receive a saline (salt water) injection. You will then complete a physical therapy course for 4-6 weeks. At 2 weeks, 4 weeks, and 6 weeks, we will be contacting you to complete the pain scales again. You will also be scheduled for a follow-up appointment at 4 weeks.

Possible Benefits
This research may or may not benefit you directly. It is possible that receiving PRP may help improve the healing of your MCL tear. Additionally, knowledge gained from the results may help us to better understand the potential benefit of platelet-rich plasma (PRP) in the treatment of Medial Collateral Ligament (MCL) tears.

Possible Risks

Your part in this research study may involve risks associated with intra-articular injection procedures. Currently, studies have shown a 1 in 70,000 risk of an infection in the knee joint following an intra-articular injection. However, proper sterile technique has been shown to decrease incidence of infections caused by knee injections and will be used during your injection.

There is also slight risk regarding the confidentiality of your participation in this study, if information about you becomes known to persons outside this study. The researchers are required to keep your study information confidential, however, so the risk of breach of confidentiality is very low.

Privacy / Confidentiality

To protect your confidentiality, your name and other identifying information will not be recorded on any study documents. You will be assigned a study number and the code linking your number with your name will be stored in secure, encrypted computer system. We will only collect information that is needed for research. Only the researchers involved in this study and those responsible for research oversight will have access to the information you provided.

Except as permitted by law, your health information will not be released in an identifiable form outside of the Yale University research team and collaborating researchers’ institution. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Note, however, that your records may be reviewed by those responsible for the proper conduct of research such as the Yale University Human Research Protection Program, Yale University Human Subjects Committee or representatives of the U.S. Department of Health and Human Services. The information about your health that will be collected in this study includes: date of birth, age, sex, history of bleeding disorders and anticoagulation status.

Information may be re-disclosed if the recipients are not required by law to protect the privacy of the information. At the conclusion of this study, any identifying information related to your research participation will be destroyed, rendering the data anonymous.

By agreeing to participate in this study, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.
This authorization to use and disclose your health information collected during your participation in this study will never expire.

**Voluntary Participation**

Participation in this study is completely voluntary. You are free to decline to participate, to end participation at any time for any reason, or to refuse to answer any individual question at any time. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). By providing verbal consent, you have not given up any of your legal rights.

*Questions*

*You have heard the above description of the research study. You have been told of the risks and benefits involved and, at this point, all of your questions regarding the study have been answered.*

**Authorization**

I have read (or someone has read to me) this form and have decided to continue to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this form.

Name of Subject: ______________________________

Signature: ____________________________________

Date: ________________________________________

____________________________________________  __________________________
Signature of Person Obtaining Consent         Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Samantha Smith MD or Maddie Kratz PA-SII. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions, offer input, discuss situations in the event that a member of the research team is not available, or if you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688.
Appendix E: Demographic Screening Survey

Demographic/Screening Survey

Name: __________________________  Today’s date: ____________________

1. Date of Birth: ___ / ___ / ____
2. Age: _____ years old

Please circle your answer for the following questions:

3. Gender:  Male  Female
   a. If female, are you or could you be pregnant?
      Yes  No

4. Is your injury being followed by a workers’ compensation program?
   Yes  No

5. Injured knee:
   Left  Right

6. Have you previously injured this knee?
   Yes  No
   Injury: ________ Date of Injury: ___ / ___ / ____

7. Have you had previous knee surgery on your injured knee?
   Yes  No

8. Have you had a corticosteroid injection on this knee in the past?
   Yes  No

9. Do you have a history of anemia?
   Yes  No

10. Do you have a history of a bleeding disorder?
   Yes  No

11. Are you currently prescribed anticoagulation (Warfarin/Coumadin, Xarelto, etc.) or antiplatelet treatment (Aspirin, Clopidogrel)?
    Yes  No

12. Do you have a history of thrombocytopenia (low platelets)?
    Yes  No
Appendix F: Grade II-III MCL Non-Operative Rehabilitation Protocol

Phase timing variable based on severity of injury and patient progression. Must meet goals to progress to next phase.

<table>
<thead>
<tr>
<th>Phase 1: ~1-2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goals:</strong></td>
</tr>
<tr>
<td>1. Control swelling</td>
</tr>
<tr>
<td>2. ROM 10-90°</td>
</tr>
<tr>
<td>3. Good quad control</td>
</tr>
</tbody>
</table>

**Ambulation/Brace Use:** weight bearing as tolerated with use of crutches, use of hinged knee brace per treating physician.

**Example Exercises:**
- Frequent icing/cryotherapy
- AAROM, AROM 0-90 degrees
- Passive extension with heel on bolster or prone hangs
- Electrical stimulation in full extension with quad sets and SLR
- Quad sets, Co-contractions quads/hams
- Straight leg raise (SLR) x 3 on mat in brace
- Short arc quads
- Side-lying hip abduction exercises
- Stationary bike when tolerated

<table>
<thead>
<tr>
<th>Phase 2: ~3-4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goals:</strong></td>
</tr>
<tr>
<td>1. ROM 0-120°</td>
</tr>
<tr>
<td>2. No effusion</td>
</tr>
<tr>
<td>3. No extensor lag</td>
</tr>
<tr>
<td>4. Normal gait mechanics and full weight bearing by end of phase</td>
</tr>
<tr>
<td>5. 60% of quadriceps strength compared with contralateral side</td>
</tr>
</tbody>
</table>

**Ambulation/Brace Use:** weight bearing as tolerated, discontinue crutches when ambulating without limp and good quad control, continue use of hinged knee brace as indicated

**Example Exercises:**
- Straight leg raise (SLR) x 3 on mat in brace
- Short arc quads
- Stationary bike – progress up to 20 minutes
- Leg press (double leg)
- Hamstring curls
- Standing hip abductor strengthening
- Step ups

| Phase 3: ~4-6 weeks |
### Goals:
1. Normal stair climbing mechanics
2. 80% of quadriceps strength compared with contralateral side

**Ambulation/Brace Use:** may discontinue use of brace when cleared by physician for ADLs

**Example Exercises:**
- Continue exercises in phase 2 and add
- Stationary bike – continue to add resistance
- Elliptical trainer
- Jogging (straight ahead only)
- Leg press (single leg)
- Single leg balance exercises
- Hip adductor strengthening

### Phase 4: ~6-8 weeks

**Goals:**
1. Good kinetic control with closed chain exercises and impact drills

**Ambulation/Brace Use:** use of brace permitted during sports

**Example Exercises:**
- Continue balance and proprioceptive training
- Single leg strengthening exercises
- Plyometrics
- Lateral and sport specific movements
Appendix G: Primary Outcome Scale Definitions

Victorian Institute of Sports Assessment-Patellar Questionnaire (VISA-P)

VICTORIAN INSTITUTE OF SPORT

1. For how many minutes can you sit pain free?

   0 mins □ □ □ □ □ □ □ □ □ □ 100 mins Points □

   0 1 2 3 4 5 6 7 8 9 10

2. Do you have pain walking downstairs with a normal gait cycle?

   strong severe □ □ □ □ □ □ □ □ □ □ no pain Points □

   0 1 2 3 4 5 6 7 8 9 10

3. Do you have pain at the knee with full active non-weightbearing knee extension?

   strong severe □ □ □ □ □ □ □ □ □ □ no pain Points □

   0 1 2 3 4 5 6 7 8 9 10

4. Do you have pain when doing a full weight bearing lunge?

   strong severe □ □ □ □ □ □ □ □ □ □ no pain Points □

   0 1 2 3 4 5 6 7 8 9 10

5. Do you have problems squatting?

   Unable □ □ □ □ □ □ □ □ □ □ no problems Points □

   0 1 2 3 4 5 6 7 8 9 10

6. Do you have pain during or immediately after doing 10 single leg hops?

   strong severe □ □ □ □ □ □ □ □ □ □ no pain Points □

   0 1 2 3 4 5 6 7 8 9 10

7. Are you currently undertaking sport or other physical activity?

   0 □ Not at all
   4 □ Modified training ± modified competition
   7 □ Full training ± competition but not at same level as when symptoms began
   10 □ Competing at the same or higher level as when symptoms began
8. Please complete EITHER A, B or C in this question.

• If you have no pain while undertaking sport please complete Q8a only.

• If you have pain while undertaking sport but it does not stop you from completing the activity, please complete Q8b only.

• If you have pain that stops you from completing sporting activities, please complete Q8c only.

8a. If you have no pain while undertaking sport, for how long can you train/practise?

<table>
<thead>
<tr>
<th>NIL</th>
<th>1-5 mins</th>
<th>6-10 mins</th>
<th>7-15 mins</th>
<th>&gt;15 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>14</td>
<td>21</td>
<td>30</td>
</tr>
</tbody>
</table>

OR

8b. If you have some pain while undertaking sport, but it does not stop you from completing your training/practice for how long can you train/practise?

<table>
<thead>
<tr>
<th>NIL</th>
<th>1-5 mins</th>
<th>6-10 mins</th>
<th>7-15 mins</th>
<th>&gt;15 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>10</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

OR

8c. If you have pain which stops you from completing your training/practice for how long can you train/practise?

<table>
<thead>
<tr>
<th>NIL</th>
<th>1-5 mins</th>
<th>6-10 mins</th>
<th>7-15 mins</th>
<th>&gt;15 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

TOTAL VISA SCORE
**Victorian Institute of Sports Assessment-Achilles (VISA-A)**

The VISA-A questionnaire: An index of the severity of Achilles tendinopathy

**IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION**

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

<table>
<thead>
<tr>
<th>100 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 mins</td>
</tr>
</tbody>
</table>

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

<table>
<thead>
<tr>
<th>strong severe pain</th>
<th>no pain</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours? (If unable to walk on flat ground for 30 minutes because of pain, score 0 for this question).

<table>
<thead>
<tr>
<th>strong severe pain</th>
<th>no pain</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Do you have pain walking downstairs with a normal gait cycle?

points

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

points

6. How many single leg hops can you do without pain?

points

7. Are you currently undertaking sport or other physical activity?

points

0 □  Not at all

4 □  Modified training ± modified competition

7 □  Full training ± competition but not at same level as when symptoms began

10 □  Competing at the same or higher level as when symptoms began
8. Please complete **EITHER A, B or C** in this question.

- If you have **no pain while undertaking Achilles tendon loading sports** please complete **Q8a only**.
- If you have **pain while undertaking Achilles tendon loading sports but it does not stop you from completing the activity**, please complete **Q8b only**.
- If you have **pain that stops you from completing Achilles tendon loading sports**, please complete **Q8c only**.

A. If you have **no pain** while undertaking **Achilles tendon loading sports**, for how long can you train/practise?

<table>
<thead>
<tr>
<th></th>
<th>NIL</th>
<th>1-10 mins</th>
<th>11-20 mins</th>
<th>21-30mins</th>
<th>&gt;30 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>7</td>
<td>14</td>
<td>21</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

**OR**

B. If you have some pain while undertaking **Achilles tendon loading sport**, but it does not stop you from completing your training/practice for how long can you train/practise?

<table>
<thead>
<tr>
<th></th>
<th>NIL</th>
<th>1-10 mins</th>
<th>11-20 mins</th>
<th>21-30mins</th>
<th>&gt;30 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>14</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

**OR**

C. If you have **pain that stops you** from completing your training/practice in **Achilles tendon loading sport**, for how long can you train/practise?

<table>
<thead>
<tr>
<th></th>
<th>NIL</th>
<th>1-10 mins</th>
<th>11-20 mins</th>
<th>21-30mins</th>
<th>&gt;30 mins</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE ( /100) %**
Western Ontario and McMaster Universities Osteoarthritis Index

### WOMAC Survey Form

Name: ___________________________

**Instructions:** In Sections A, B, and C, questions will be asked about your hip or knee pain. Please mark each response with an X. If you are unsure about how to answer a question, please give the best answer you can.

**A. Think about the pain you felt in your hip/knee during the last 48 hours.**

<table>
<thead>
<tr>
<th>Question: How much pain do you have?</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Walking on a flat surface</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Going up and down stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. At night while in bed, pain disturbs your sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Sitting or lying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Standing upright</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B. Think about the stiffness (not pain) you have in your hip/knee during the last 48 hours.** Stiffness is a sensation of decreased ease in moving your joint.

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. How severe is your stiffness after first awakening in the morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. How severe is your stiffness after sitting, lying, or resting in the day?</td>
<td></td>
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</tr>
</tbody>
</table>

**C. Think about the difficulty you had in doing the following daily physical activities due to your hip/knee during the last 48 hours.** By this we mean your ability to move around and look after yourself.

<table>
<thead>
<tr>
<th>Question: What degree of difficulty do you have?</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Descending stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Ascending stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Rising from sitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Standing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Bending to the floor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Walking on flat surfaces</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Getting in and out of a car, or on or off a bus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Going shopping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Putting on your socks or stockings</td>
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<tr>
<td>17. Rising from the bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Taking off your socks or stockings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>19. Lying in bed</td>
<td></td>
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<tr>
<td>20. Getting in or out of the bath</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>21. Sitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Getting on or off the toilet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Performance heavy domestic duties</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Performing light domestic duties</td>
<td></td>
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</tr>
</tbody>
</table>
Appendix H: Qualtrics Visual Analog Scale (VAS) Scores Survey

What is your study participant ID number?

What week are you filling out this survey?

- Week 2
- Week 4
- Week 6

On a scale of 1-10, how much pain are you experiencing in your knee?

No pain 0 1 2 3 4 5 6 7 8 9 10

Slide the bar to the number that most closely describes your pain at this moment.

Appendix I: Qualtrics Return to Activity Survey

Is this your week four or week eight survey? (Four or eight weeks after the injection?)

- 4 weeks
- 8 weeks

Have you returned fully to your baseline activity? (This is defined as pain free participation in the activities/sports you engaged in prior to injury)

- Yes
- No

If you answered yes to the previous question, on what date did you return to all activity?

Is this your week four or week eight survey? (Four or eight weeks after the injection?)

- 4 weeks
- 8 weeks

Have you returned fully to your baseline activity? (This is defined as pain free participation in the activities/sports you engaged in prior to injury)

- Yes
- No
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