A Randomized, Control Clinical Trial: The Effect of Different Injection Regimens of Autologous Conditioned Plasma for the Treatment of Symptomatic Knee Osteoarthritis

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Title: A Randomized, Control Clinical Trial: The Effect of Different Injection Regimens of Autologous Conditioned Plasma for the Treatment of Symptomatic Knee Osteoarthritis

Principal Investigator: Adam Anz, M.D.

Co-Investigators: Roger Ostrander, M.D.

Steve Jordan, M.D.

Christopher O'Grady, M.D.

Brett Kindle, M.D.

Hillary Plummer, PhD, ATC

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Institution(s): Andrews Institute
1040 Gulf Breeze Pkwy.
Gulf Breeze, FL 32561
(850) 916- 8761

1 Background / Scientific Rationale

In the United States it is estimated that 47 million people have been diagnosed with arthritis. 4.3 million have been diagnosed with isolated osteoarthritis of the knee and knee arthritis accounts for 20% of disability claims [1]. Prevalence of the disease continues to climb and is expected to double by 2030. In addition, 4 out of 5 patients with osteoarthritis have movement limitations [1]. Currently there are no curative treatments for osteoarthritis. Surgical options include arthroscopy, osteotomies, and total joint replacement, but not all patients with knee osteoarthritis are candidates for surgical treatments, and others choose non-operative treatments instead of undergoing a procedure. Non-surgical treatment options include medications such as non-steroidal anti-inflammatory's (NSAIDs), injectables such as corticosteroids and hyaluronic acid, or physical treatments such as rehabilitative therapy, unloading braces, and activity modifications (i.e. canes or walkers). Additionally, weight loss can help in the battle to reduce pain in cases of knee osteoarthritis.

The clinical efficacy of hyaluronic acid or corticosteroid injections has been reported, but effects are short lived. This has led to the development of additional injection options such as autologous derived blood products which have been documented to alleviate symptoms related to knee osteoarthritis, with recent comparative studies suggesting a greater, long-lasting effect with these blood derived products like platelet rich plasma (PRP) [2-8]. One clinically-developed preparation of platelet rich plasma, named autologous conditioned plasma (ACP), has randomized controlled trial data proving efficacy [4,9]. Clinical use of platelet rich plasma for knee arthritis typically involves a 3-injection series over 3 weeks, i.e. an injection once a week for three weeks. Currently, all three orthopedic providers in this study use ACP to treat patients with knee osteoarthritis in common accepted clinical practice.

2 Objectives

The main objective of this study is to determine if hyaluronic acid (HA) injected at the same time as autologous conditioned plasma (ACP), a leukocyte-poor platelet rich plasma product, will improve the performance of ACP in the treatment of symptomatic knee osteoarthritis. We hypothesize that the injection of hyaluronic acid will improve the efficacy of ACP.

3 Participant Eligibility

Inclusion Criteria: Patients between the ages of 30 and 80 who have documented radiographic evidence of OA in the tibiofemoral or patellofemoral compartment of the target knee (Kellgren-Lawrence grades 1-4) will be screened for participation in this study. Patients must have a documented diagnosis of primary OA for at least 6 weeks.

Exclusion criteria: Patients who have had viscosupplementation in the involved knee in the past 6 months. Any patient who has had a corticosteroid injection in any joint within 3-months prior to screening will be excluded. Patients with gout or rheumatologic disease will be excluded. Patients who have had a previous negative experience with HA. Any patient who will have difficulty obtaining internet access, does not have an active e-mail address, or is unable to comprehend study documents or give informed consent will be excluded.

4 Participant Enrollment

80 patients will be recruited through the Andrews Institute physician practices. Potential participants will be prescreened for inclusion and exclusion criteria through standard of care medical evaluations. Once a potential participant has agreed to be involved in the study, they will go through the described informed consent process. Patients meeting the inclusion criteria will have the study explained to them by one of the members of the investigating team, and they will be given an opportunity to participate if they are interested. No specific advertising or recruitment material will be utilized.

Participant will also be instructed that they must not take any prescription or over the counter non-steroidal anti-inflammatory drugs (NSAIDS) for 1 week prior to the first injection until after the final injection. The participants will then be randomly placed in one of the two study groups and be scheduled to receive a three-injection series of autologous conditioned plasma injection or a two-injection series of autologous conditioned plasma and hyaluronic acid and a third injection on the third week of ACP in their involved knee. For The group receiving autologous conditioned plasma and hyaluronic acid, HA will be an additional injection on the first two injections and the third injection will be ACP alone. This regimen was selected to reflect the current evidence-based regimens for ACP and HA independently.

5 Study Design and Procedures

Study design will be randomized control trial. Participants who meet the inclusion criteria will have the study explained in detail and informed consent will be obtained as outlined above. Participants will complete patient reported outcome questionnaires prior to their injection. The questionnaires will include the Western Ontario and McMaster University‘s Osteoarthritis Index (WOMAC), International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS). The WOMAC is 24 questions and takes approximately 2-5 minutes, the IKDC is 19 questions and takes 3-5 minutes, and the KOOS is 42 items and takes approximately 5-10 minutes. Participants will also complete these questionnaires at 1, 3, 6, 12, 18, and 24 months after the final injection.

A trained medical professional will draw blood from the patients arm and the blood will be spun in a centrifuge for 5 minutes at 1500 RPM. The platelets will then be separated off for injection into the patient's knee. The treating physician will then inject the ACP into the involved knee joint following standard aseptic technique per the physician's standard of care. This entire process will be completed in a single patient visit. Any unused portion of a sample in the physician's office will be disposed of through standard biohazard waste disposal systems as required by law.

Group 1 [ACP]: Will receive 3 intra-articular injections of autologous conditioned plasma dosed at once a week for 3 weeks. Group 2 [ACP-HA]: Will receive 2 intra-articular injections of autologous conditioned plasma and hyaluronic acid once a week for 2 weeks and a third injection on the third week of ACP.

6 Expected Risks and Benefits

Risks and Discomforts: Potential risks include those expected with any injection including syncope, dizziness, headache, nausea, tachycardia, infection (septic arthritis, phlebitis, and osteomyelitis), bleeding, or pain. Additionally, participants may experience knee stiffness or inflammation associated with the procedures. These risks would not be any higher with the test interventions than those patients are subject to with injection treatments of knee OA. As with any research involving patients there is the inherent risk of a breach in patient confidentiality though this will be minimized through the use of participant code numbers and adherence to all HIPAA guidelines.

Benefits: Direct benefits of the study include injections that may provide potential pain relief, improvement of knee function, and improvement of quality of life, which all could lead to the avoidance of surgical intervention. It is also believed that the information obtained in this study will help advance treatment of osteoarthritis through the use of regenerative medicine.

7 Data Management Procedures

All personal information is strictly confidential and no names will be disclosed except as required by law. All information and data collected during this research will be recorded in a spreadsheet. This spreadsheet will not contain protected health information. The spreadsheet will be stored in a secure password protected folder on a laptop that only the study Investigators will have access to and will be permanently deleted following publication of any and all manuscripts, if any, written as a result of this research. Records related to this study will be securely retained

in a secure location for a period of 3 years after the completion of the study or longer as required by law. At that time, all records will be properly destroyed.

8 Data Analysis

All data will be entered into Surgical Outcomes System (SOS) & Research Electronic Capture Database (REDCap) and descriptive data will be compiled.

9 Statistical Considerations

A power analysis was performed to determine sample size based upon recent clinical trials comparing PRP to HA for the treatment of osteoarthritis. Analysis utilized the average of standard deviation to detect average of group mean effect at 80% power. This determined that 25 patients per group would be needed to reach statistical significance with the WOMAC.

Ranges, means and standard deviations for all measures will be determined and calculated. Data will be analyzed for differences between groups using a repeated measures ANOVA design, using a significant p-value of < 0.05 for rejecting the null hypothesis.

10 Quality Control and Assurance

All protocols will be monitored and analyzed data will be checked for accuracy by the principal investigator and /or a designated AREF research team member. All medical data will be kept in compliance with HIPAA guidelines.

11 Regulatory Requirements

Informed Consent:

The informed consent process will be performed by one of the study investigators or staff, in the office. All participants will have the study described to them and will give as much time as they require to read an approved, stamped version of the informed consent document. After signing of the informed consent document, participants will be given a copy for their records. This process will take place only after the patient has consented to proceed with the study.

Participant Confidentiality:

Participant confidentiality information is listed above in #7 (Data Management Procedures). All medical data will be recorded and stored in compliance with HIPAA guidelines.

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