Official title: Microfragmented Adipose Tissue Versus Platelet-rich Plasma for Knee Osteoarthritis: a Randomized Comparative Trial

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Platelet-rich plasma versus Adipose-derived stem cell for knee osteoarthritis: A randomized, comparative trial

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Background

Knee osteoarthritis is a leading cause of disability worldwide.[1,2] Standard of care treatments for knee OA include activity modification, weight loss, therapeutic exercise and injections like corticosteroids and viscosupplement. These commonly used non-operative treatments focus on symptom palliation, but are not disease modifying.[3]

Orthobiologics have emerged as a promising treatment for knee OA. The most widely studied orthobiologic is platelet-rich plasma (PRP).[4] PRP is a dense concentration of platelets derived from autologous whole blood and platelets are concentrated 2-5x compared to baseline.[5] The platelets have demonstrated anti-inflammatory and chondroprotective properties.[6] PRP has been shown superior to placebo and viscosupplement for knee OA in several clinical trials.[7-10]

While PRP is the most widely studied and used orthobiologic, it contains only platelets, but no mesenchymal stem cells. Therefore, a simple, office-based intervention able to collect stem cells to treat knee OA would be ideal. Adipose (fat) is a known source of mesenchymal stem cells and it can be easily and safely aspirated in the clinic.[11] The adipose tissue aspiration and processing is accomplished through a simple process. After local anesthesia to the site of adipose aspiration (lower abdomen or buttock), 30ml of adipose is aspirated through a cannula. That adipose is then processed in accordance with FDA guidelines including minimal manipulation (adipose only goes through a short, simple centrifugation to remove oils and leaves behind the fraction that contains mesenchymal stem cells).[12] Using of minimally manipulated, adipose derived stem cells has been shown safe for use as injection therapy for knee OA for 3 years.[13,14]

Aim: To conduct a randomized trial comparing the clinical outcomes of PRP (standard intervention) versus Adipose-derived stem cells (investigational).

Hypothesis: Both interventions will result in significant improvement in patient-reported outcomes. We hypothesize that adipose-derived stem cells will provide superior outcomes.

Methods:

Participants **/ Outcome Measures / Sample size**: Participants with symptomatic knee OA will be recruited from the sports medicine and orthopedics clinics, as well as advertising flyers within the clinic.

Inclusion / Exclusion Criteria

Inclusion criteria

Age 25-75 years

BMI < 40

Diagnosis of knee OA (primary and post-traumatic)

(Note: Participant may have OA in both knees, but only the most symptomatic knee will be treated as part of this trial so that patient reported outcomes are clearly defined for a single joint. The non-study knee may undergo all usual care prior to enrollment in the study, but no additional interventions can be performed during the course of the trial. If participant requires additional treatment, the participant will be unenrolled in the study).

Radiographic evidence of OA of the target knee (Kellgren-Lawrence grades 1-4)

Continued OA pain in the target knee despite at least 6 weeks of 1 of the following nonoperative treatments: activity modification, weight loss attempt, physical therapy, or NSAID / acetaminophen.

Knee Osteoarthritis Outcomes Score (KOOS)-Pain subscale 20-65

Working knowledge of English language (to be able to complete all outcome scores)

Ability to attend all follow-up appointments

Exclusion criteria

Isolated patellofemoral OA

3+ effusion of the target knee (stroke test grading system)

Significant (10 degree) valgus or varus deformities

Prior injection therapy:

- Steroid injection in target knee in the last 3 months
- Viscosupplementation in target knee in the last 6 months
- PRP in the target knee in the last 1 year
- Cellular treatments in index knee (bone marrow, amniotic suspensions etc) all time
- Participation in any experimental device or drug study within 1 year before screening visit

Oral or IM steroids for last 3 months

Medical condition that may impact outcomes of procedure including:

- anemia
- thrombocytopenia
- bleeding disorders
- inflammatory disorders like rheumatoid arthritis, lupus
- diabetes
- any history of cancer (other than non-melanoma skin malignancies)
- taking anticoagulants (aspirin, Plavix, eliquis, Xarelto, warfarin, lovenox)

Taking immunosuppressants, having a severe systemic infection

Previous cartilage repair procedure on the injured cartilage surface (ie, OATS, ACI, MFX)
Previous surgery at the target knee within the past 1 year
Any degree of cognitive impairment.
OA of either hip
Pregnancy, lactating, or intent to become pregnant during treatment period
Gout
History of infection or current infection at the affected joint
Smoking

Sample Size Calculation:
A total of 88 (44/group) participants will complete this two-treatment parallel-design study. The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 9 units. This is based on the assumption that the standard deviation of the response variable is 15.

We will enroll 110 (55/group) participants to ensure that 88 complete their 6 month visit assuming 80% follow up at the primary endpoint of the study.

Outcomes and Follow Up

Demographics collected
Age
Body mass index
Race
OA grade (as determined by KL stage on x-rays)
MRI severity (only if MRI within 1 year exists; no additional MRI will be ordered if participant **does not have it) as determined by MOAKS score**

The following outcomes will be collected at baseline,1,3,6, and 12 months.
Adverse events
KOOS
VAS Pain (with ADLs)
Tegner
Additional baseline only measures: knee pain diagram and the pain catastrophizing scale
Additional 6 and 12 month only measures: failure (defined by failure to improve KOOS-P score, desire to seek additional treatment including injections or surgery) with failure at 6 months representing the primary outcome variable.

Follow-up plan:

All participants' first visit will be standard of care to provide a medical evaluation and assess best treatment plan for that participant , regardless of candidacy for this study. This evaluation includes x-rays of their knees as a standard part of the evaluation. This will be billed through insurance. If they meet criteria and choose to enroll, their procedure and all follow up visits will be covered by the research study funds. The schedule will be as follows (by group):

PRP:

1) Baseline (at time of enrollment during initial clinical evaluation, billed to insurance as standard evaluation, RedCap surveys administered in clinic)
2) Injection (REDCap surveys in clinic)
3) 1 month (REDCap surveys in clinic)
4) 3 months (REDCap surveys in clinic)
5) 6 months (REDCap surveys in clinic)
6) 12 months (REDCap surveys in clinic)

Adipose:

1) Baseline (at time of enrollment during initial clinical evaluation, billed to insurance as standard evaluation, RedCap surveys)
2) Injection
3) 2 weeks (in clinic wound-check, covered by research fund, no surveys)
4) 1 month (REDCap surveys in clinic)
5) 3 months (REDCap surveys in clinic)
6) 6 months (REDCap surveys in clinic)
7) 12 months (REDCap surveys in clinic)

Primary outcome: KOOS-Pain 6 months

Data will be housed in RedCap on a password protected, location secured medical center computer.

This study will utilize REDCap (Research Electronic Data Capture), a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store data. The Ohio State Center for Clinical and Translational Science (CCTS) Research Informatics Services will be used as a central location for data processing and management. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter (640 Ackerman Road; Room 345)

REDCap instance is located on an internal OSUWMC network. Remote access to this network can be obtained over an encrypted VPN tunnel (AnyConnect). This VPN uses

Protocol: DTLS and Cipher: RSA_AES_128_SHA1. Background checks are performed on all staff that are on the network or obtaining VPN access.

Randomization
Participants will be randomized using randomization function available in RedCap.

Statistics

Continuous variables will be checked for normality and subsequently compared using either unpaired t-tests (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data) at 6 months for the primary outcome. The variables will be analyzed again at 12 months..

After randomization, participants , medical staff and research team will note treatment arm allocation.
All participants will receive the following pre-procedural instructions

Avoid non-steroidal anti-inflammatories (NSAIDs) and aspirin for 14 days before the procedure.

No exercise the day before and the day of the procedure

Arrive to the procedure well-hydrated

Procedural Details
Platelet rich plasma
157mL of whole blood will be harvested via standard venipuncture from the antecubital fossa and mixed with 24mL ACD-A (manufacturer recommends 8mL ACD-A per 52mL of whole blood). 156ml of whole blood will be processed in the FDA Cleared Angel cPRP system at 2% hematocrit.

1ml of whole blood and the resultant PRP will be analyzed in the Sysmex XN-350 for complete analysis (platelet, leukocyte [total and differential], red blood cell counts). This data will be housed in the same RedCap system. The PRP left over after the Sysmex testing will be frozen in de-identified tubes in the -80C degree freezer on the 2nd floor of the Jameson Crane Sports Medicine Institute which is locked and only study staff have access to. At the conclusion of the study, this PRP will be thawed and sent for growth factor quantification (measuring transforming growth factor, platelet derived growth factor and interleukin-1). This analysis requires that all samples be completed in a single batch. For that reason, all samples will be kept in the freezer until the end of the study.

The remaining PRP (estimated 4-6mL) will be injected under sterile technique using ultrasound-guidance through a superolateral approach. For participant comfort, 2mL of 1% lidocaine can be administered using a 26-gauge needle (into soft tissues only). PRP will then be injected using a 25-guage needle. A maximum of 6ml of PRP will be injected. Injection site will be cleaned and bandaged and participant will be dismissed with post-injection precautions and 1 month follow-up scheduled.

Adipose-derived stem cell

Adipose will be aspirated from the subcutaneous tissue of the buttock or abdomen (depending on best available specific to each participant). Once the area is prepared using standard sterile precautions, the aspiration site will be injected with 10ml 1% lidocaine with epinephrine. A small poke incision will be made with an 11-blade scalpel (to allow for aspiration cannula to be easily inserted). Then 120ml of Klein solution will be injected into the adipose tissue (facilitates ease of aspiration). Solution will sit for 15 minutes to allow for adequate anesthesia. Aspiration cannula will be inserted and carefully moved in a back and forth motion for 2 minutes to allow for ease of adipose aspiration. Then under continued sterile conditions, 30ml fat will be aspirated using13G cannula. Aspiration site will be cleaned and bandaged. The aspirated fat will be immediately processed using the Lipogems system ™ (Lipogems, Norcross, GA). This is a FDA cleared device that efficiently processes adipose to remove oil and leave mesenchymal stem cells for injection. Briefly, the 30ml of adipose is transferred to the device, saline is run through the device to remove oils and then approximately 5-7ml of adipose tissue is removed and ready for injection. This isolates the fraction of tissue that contains stem cells. The adipose derived cells are then injected in identical fashion to the PRP above (except an 18-gauge needle will be used for the injection due to higher viscosity).

0.5ml of adipose derived stem cells will be analyzed in the comparative orthopedics laboratory for total stem cell count and viability.

For both groups, if there is excess synovial fluid (an effusion), this will be removed (standard of care) prior to injecting the PRP or ADSC. This synovial fluid will be immediately analyzed for a complete blood count and then frozen in de-identified tubes in a locked -80C freezer on the second floor of the Jameson Crane Sports Medicine Institute. Only approved study staff will have access to this. At the conclusion of the study, all frozen samples will be analyzed for inflammatory proteins (IL-1, IL-8, TNF) This analysis requires that all samples be completed in a single batch. For that reason, all samples will be kept in the freezer until the end of the study.

Aftercare

Tylenol and ice are permissible for immediate pain control.
In the event of a post-injection flare (a possible risk), over-the-counter NSAIDs will be permitted until the flare resolves (standard of care).
No impact lower limb activity (running, lifting) for the first 1 week. Afterwards, activity as tolerated is encouraged.

Compensation

Participants will be compensated for their time with a 20-dollar gift card at the injection visit and the 1,3, 6 month and 12 month follow up visits.

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