Clinical Evaluation of Autologous Micro-Fragmented Adipose Tissue as a Treatment Option for Meniscus Tears

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Lipogems SPO

PURPOSE

The purpose of this study is to explore the potential of Lipogems micro-fragmented adipose tissue as a meaningful treatment option for meniscus tears.

STUDY DESIGN

We propose a non-randomized, single site, prospective study of 20 subjects to evaluate the effects of non-digested micro-fragmented adipose tissue (Lipogems) on patients with evidence of a meniscus tear where there may also be osteoarthritis.

Patients will be treated with Lipogems by intra articular meniscal and joint injection under ultrasound guidance and evaluated using follow up function questionnaires, physical examination and MRI imaging.

BACKGROUND

Osteoarthritis is a joint disease that mostly affects cartilage. Cartilage is the slippery tissue that covers the ends of bones in a joint. Healthy cartilage allows bones to glide over each other. It also helps absorb shock of movement. In osteoarthritis, the top layer of cartilage breaks down and wears away. This allows bones under the cartilage to rub together. The rubbing causes pain, swelling, and loss of motion of the joint. Also, bone spurs may grow on the edges of the joint. (1).

Meniscus tears are among the most common knee injuries. Athletes, particularly those who play contact sports, are at risk for meniscus tears. However, anyone at any age can tear a meniscus. When people talk about "torn cartilage" in the knee, they are usually referring to a torn meniscus.

Sudden meniscus tears often happen during sports or other activities. Older people are more likely to have degenerative meniscus tears. Cartilage weakens and wears thin over time. Aged, worn tissue is more prone to tears. Just an awkward twist when getting up from a chair may be enough to cause a tear, if the menisci have weakened with age (2).

Standard treatment for meniscal tears include: rest, ice, anti-inflammatory and physical therapy. For persistent pain and swelling, patients are often given an injection of corticosteroid and/or hyaluronic acid. Unfortunately, many patients have persistent pain, swelling and limitations on activities of daily living and are then offered arthroscopic surgery which involves resecting and debriding the worn or torn piece of meniscus referred to as arthroscopic partial meniscetomy (APM). Recent well designed studied have questioned the effectiveness of this treatment which includes randomized studies where a "sham" procedure is performed. These studies have shown that APM is no better than physical therapy nor was it superior to the sham surgery. In addition, APM has been shown to accelerate the degenerative process in the knees of patients who also have early arthritis of their knee. None-the-less, many people continue to suffer with ongoing pain and many will then proceed to even greater surgery which includes total knee replacement (TKR) and great economic costs as well as the potential for complications, long rehabilitation, etc. Therefore, an effective and noninvasive treatment for patients with continuous knee pain related to meniscal tears meniscus is greatly needed.

There are a few studies that have demonstrated the potential benefit of using a patient's own biologic product such as platelet-rich plasma (PRP) and their own stem cells. Several studies have used bone marrow and others have used adipose tissue that is harvested directly from the patient.

Here, we present a study, highlighting the safety and the potential reparative and regenerative mechanisms in the treatment of damaged knee joints by percutaneous injection using real time continuous ultrasound imaging into the knee joint and menisci with Lipogems autologous micro-fragmented, non-digested adipose tissue containing bioactive and regenerative elements (3).

THE KNEE JOINT

The knee joint joins the thigh with the leg and consists of two articulations: one between the femur and tibia, and one between the femur and patella. It is the largest joint in the human body and

perhaps the most clinically challenging. The knee joint is vulnerable to acute injury as well as the development of progressive degenerative changes.

MENISCUS

The menisci of the knee are two fibrocartilaginous tissue pads which serve to disperse friction in the knee joint between the lower leg or tibia and the upper leg or femur. Each knee joint has two menisci. One is in the medial knee and the other in the lateral knee. They are semi-lunar in shape and are attached to small depression in the tibia and between the condyles of the tibia (intercondyloid fossa), and towards the center they are unattached and their shape narrows to a thin shelf. The blood flow of the meniscus is from the periphery (outside) to the central meniscus. Blood flow decreases with age and the central meniscus is avascular by adulthood leading to very poor healing rates (4).

The menisci act to disperse the weight of the body and reduce friction during movement. Since the condyles of the femur and tibia meet at one point which changes during range of motion, the menisci spread the load of the body's weight.

Meniscal damage is diagnosed by magnetic resonance imaging (MRI) scans. Clinical information can be gleaned by diagnostic musculoskeletal ultrasound to provide detailed imaging of the meniscus anteriorly, however, is not considered diagnostic of meniscal tears.

CURRENT STANDARD OF CARE AND TREATMENT OPTIONS

There are currently very few options for treatment of osteoarthritis with tears in the medial or lateral meniscus in the knee.

1. *Lifestyle Modification*

Reduced activity and weight loss to relieve stress and pressure on the affected knee.

2. *Physical Therapy*

Manual therapies and supervised exercises to strengthen, increase range of motion and bracing to improve functional abilities to reduce the joint pain.

3. *Exercises to Strengthen the Knee and Relieve Pain*

Exercises designed to strengthen the supporting structures of the knee to relieve strain and pain.

4. *Medications for Treatment of Knee Pain and Arthritis*

Non-steroidal anti-inflammatory drugs NSAIDS to reduce inflammation and relieve pain.

5. *Injections and Procedures for Knee Pain*

Cortisone injections are often recommended to relieve inflammation. Platelet Rich Plasma a treatment whereby growth factor from plasma are concentrated and injected to stimulate the repair mechanisms (2).

6. *Knee Surgery*

If knee pain persists, surgery may be the option. Different knee surgeries include knee replacements and knee arthroscopy (5).

When such conservative treatment fails, and arthroscopic procedures are administered the efficacy has not been well established. The major drawback of the arthroscopic procedures is accelerated osteoarthritis (6) (7).

Recently the use of concentrated growth factors from patient blood called platelet rich plasma has been studied and numerous publications have been emerging with varying degrees of success (3).

Arthroscopic repair of the damaged meniscus may be recommended. However, the current treatment with arthroscopic surgery and meniscectomy, even with partial one, is associated with accelerated osteoarthritis in the already afflicted knee (8).

Therefore the lack of a non-invasive treatment to improve joint function and preserve joint structure in the damaged knee joint presents a major therapeutic challenge.

The purpose of this study is to explore the potential of Lipogems micro-fragmented adipose tissue as a meaningful treatment option.

There are many applications of biologic preparations in treating musculoskeletal conditions and often several are combined. With this comes the inherent inability to assess the impact of each biological on outcomes and the conclusions subsequently drawn.

For the purpose of this study, Lipogems in its processed form will be used without combining any other biological or pharmacologic elements to the treatment.

ANIMAL STUDIES

Autologous stem cells have been demonstrated to be extraordinarily effective in treating animals with arthritis. Several veterinary stem cell companies are now in operation, utilizing adipose derived stem cells (SVF) to accelerate healing in horses as well as provide regenerative therapy for osteoarthritic dogs. Vet-Stem (www.Vet-Stem.com) has treated more than 10,000 animals since 2003 (9) and published data showing efficacy in double blinded studies of canine osteoarthritis, showing statistically significant improvements in lameness, range of motion, and overall quality of life (10).

RATIONALE

We have seen evidence that is capable of exhibiting significant anti-inflammatory effects, which may subsequently provide some relief from the pain associated with. fat graft containing reparative tissue. We intend to examine whether a direct injection of Lipogems micro fractured adipose tissue can provide an effective treatment option and an alternative to arthroscopic surgery in the treatment of meniscus tears.

STUDY OBJECTIVES

To evaluate the use of Lipogems, micro-fractured adipose tissue, in soft tissue defects of the meniscus.

INCLUSION CRITERIA

(1) Age 35 and older
(2) Symptoms consistent with torn meniscus (at least one of clicking popping, giving way, pain with pivot or torque, pain that is episodic)
(3) Pain that can be provoked by palpitation or compression of the joint line.
(4) Pain located in the medial joint line that has persisted for at least 3 months.
(5) MRI or arthroscopic evidence of meniscal tear.
(6) Failed conservative treatment which has included: anti-inflammatory or other medications for pain; physical therapy; injections including corticosteroid injections and/or hyaluronic acid injections. This would include patients who have been told by an orthopedic surgeon that they would be a candidate for arthroscopic partial meniscectomy.

EXCLUSION CRITERIA

(1) Chronically locked knee.
(2) Prior surgery performed on effected knee
(3) Assessment showing anything other than degenerative tears of the medial meniscus requiring surgical intervention.
(4) Recent (within 6 weeks) treatment with PRP, cortisone oral or by injection, or Hyaluronic injection.
(5) Any disease or condition the investigator feels would hinder treatment.
(6) Any contra-indication to lipoaspirate which includes: bleeding disorder, infection, pregnancy; allergy to anesthetic agents.
(7) Malignancy within the last 5 years.

STUDY PROCEDURES AND GUIDELINES

The patient is restricted from taking steroids, and nonsteroidal anti-inflammatory medications for three days prior to Lipogems treatment and for 4 weeks after Lipogems treatment.

Informed Consent: informed consent is signed by the patient prior to conducting study related activities.

PRE-TREATMENT ASSESSMENT

- MRI
- KL OA score
- Joint specific Function Scores KOOS
- VAS visual analogue pain scales
- Pre-Treatment range of motion with a goniometer

DEMOGRAPHICS

Demographic information (date of birth, gender, race) will be recorded at Screening.

MEDICAL HISTORY

Relevant medical history, including history of current disease, and information regarding underlying diseases will be recorded at Screening.

FAT HARVEST PROCEDURE

1. Informed consent is obtained.
2. Patient is placed supine on procedure table.
3. Abdomen is marked with a surgical marker in an oval demarcating the region for fat harvest.
4. Area is bordered by sterile drapes.
5. Abdomen is swabbed with Chloroprep.
6. 500cc of tumescent is prepared by combining 500cc sterile saline, 50cc 1% Lidocaine and 1cc of 1:1000 Epinephrine.
7. Using an18-gauge needle the injection site injected with anesthetic tumescent for local anesthesia and the needle tip used to slightly expand the entry point to make access for insertion of the cannula.
8. Using a17-gauge blunt end cannula the harvest site is irrigated subcutaneously penetrating below Scarpa's fascia channeling with 60cc – 120cc tumescent.
9. After waiting10-15minutes using a 13-gauge blunt end cannula adipose tissue is aspirated. (Amount of decanted fat should equal approximately a 4:1 ratio to volume necessary for final injectate).
10. Following fat harvest the injection site is cleaned and sterile bandages applied.

PROCESSING LIPOGEMS

STEP 1: The Lipogems disposable medical device is removed from sterile package and laid out on a sterile field. The Lipogems kit is assembled and connected to a bag of 1000cc sterile saline. The waste bag is connected and laid on the floor out of the way of foot traffic. The assembly is prefilled with saline solution and flushed by gravity to obtain and completely closed system free of air.

STEP 2: The syringe containing the lipoaspirate is then connected to the Lipogems device. The first step in cluster reduction is obtained as the lipoaspirate in injected into the kit passing through the first reduction filter.

STEP 3: The line from the saline bag and is opened allowing blood and oil residues to drain through the system into the waste collection bag. Then line is closed.

STEP 4:The device containing stainless steel ball bearings is shaken for thirty seconds in order to fragment and wash the lipoaspirate. Stop and allow adipose clusters to float to the top.

STEP 5: The rinsing and shaking steps are repeated until the tissue is bright yellow and the saline in the chamber is clear (strands of connective tissue may be present).

STEP 6: The device is turned 180 degrees, and a 10cc sterile syringe is attached to each end. With only the input portal (lower) opened, 10cc saline is drawn into the lower syringe. With the palm of one hand, the lower syringe is pushed upwards, forcing the washed tissue through the second reduction filter and filling the upper syringe with Lipogems.

STEP 7: The syringe is decanted, removing excess saline, and is now ready for use without any further washing or preparation.

STEPS 2-7 may be repeated by injecting additional lipoaspirated adipose tissue into the device until the desired final volume of Lipogems is obtained.

TREATMENT
Following the fat harvest and preparation of the Lipogems fat graft, diagnostic ultrasound is used to identify the target structures in coordination with historical imaging from MRI. If a large effusion is detected the effusion will be aspirated prior to the injection of Lipogems.

The injection will be performed using sterile technique. Lidocaine may be used topically, but will not be introduced into the injection site. Generally, a 22 guage needle 1.5 to 2.5 inches in length will be used depending on the patient's anatomy. The injection will be performed under direct ultrasound guidance into the hypoechoic defects within of the medial and or lateral meniscus tears. Ultrasound imaging will determine the placement of the needle tip and visualizing complete lipofilling of the soft tissue defects. All injectate volumes and locations will be recorded. The patient will remain in the supine position for 10 minutes and post-injection vital signs obtained. Post-injection guidelines will included non-weightbearing with crutches X 1 week and the weight bearing for simple daily activities, refraining from running and jumping activities and repeptitive fleion beyond 90 degrees for 4 weeks total. The patient will then be placed on a progressive strengthening program over weeks 4-6. If there is no pain, swelling; significant joint line tenderness and near full range of motion, unrestricted activities will be allowed at the 6-8 week time-frame. If there are abnormal findings of pain, tenderness; swelling etc.; the patient will be reassessed and limited in their activities for 8 weeks from the time of the procedure and then monitored for their response following this.

OUTCOME MEASURES

Follow up outcome assessment will be conducted by phone and functional questionnaires in addition to physical examination and functional measurements when in-office follow up visits are applicable. Numeric Pain Scale (NPS) and Knee Innjury and Osteoathritis Outcome Score (KOOS) will be utilized. The NPS will be a subjective measure of pain using a scale of 0 = No pain through 10 worse pain ever. This will be preferred over a visual analogue scale (VAS) as it can be given over the phone and does not necessary require the patient's presence in the clinical area. KOOS is widely used for research purposes in clinical trials, large-scale databases and registries. KOOS is also extensively used for clinical purposes. In the clinic, KOOS is used to monitor groups and individuals over time. Due to its comprehensiveness, when the questionnaire is completed prior to a consultation, it can be used to guide the consultation as to the symptoms and difficulties experienced by the patient.

KOOS is intended to be used for knee injury that can result in post traumatic osteoarthritis (OA); i.e. ACL (anterior cruciate ligament) injury, meniscus injury, chondral injury, etc.

KOOS is also used in knee OA. An advantage of the KOOS is the inclusion of two different subscales of physical function relating to daily life, and sport and recreation. This enhances the instrument's validity for patients with a wide range of current and expected physical activity levels.

KOOS is intended to be used over short- and long-term time intervals; to assess changes from week to week induced by treatment (medication, operation, physical therapy) or over years following a primary injury or OA.

KOOS can be used in research to assess groups and to monitor individuals.

KOOS' content validity was based upon a literature search, a pilot study and an expert panel (from US and Sweden) consisting of patients, orthopedic surgeons and physical therapists.

KOOS consists of 5 subscales; **Pain**, other **Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec)** and **knee related Quality of life (QOL)**. The previous week is the time period considered when answering the questions. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. A total score has not been validated and is not recommended. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. The five individual KOOS subscale scores are then given as secondary outcomes to enable clinical interpretation. Please see FAQ for further information on this procedure. The results of the 5 subscales can be plotted as an outcome profile (order of subscales from left to right: Pain, Symptoms, ADL, Sport/Rec and QOL), preferably in a graph with scores from 0-100 on the y-axis and the five subscales on the x-axis

KOOS is patient-administered, the format is user friendly, and takes about 10 minutes to complete.

KOOS is in the public domain and is free of charge. No licensing or permission to use KOOS or the other questionnaires available from www.koos.nu is required

FOLLOW UP SCHEDULE

Immediately post treatment:
NPS pain score

24 Hours
NPS pain score

One week following treatment:
NPS

Five weeks following treatment:
NPS
Function scores (KOOS)
Range of motion when in person assessment
Quadriceps strength when in person assessment

Three months following treatment:
NPS
Function scores (KOOS)
Range of motion when in person assessment

Six months following treatment:
NPS
Function scores (KOOS)
Range of motion when in person assessment
Repeat MRI

One year following treatment:
NPS
Function Scores (KOOS)
Repeat MR

INFORMED CONSENT

The risks, benefits, and alternatives discussed with patient. Patient understands all post procedure instructions and follow-ups. All questions answered to satisfaction.

VULNERABLE SUBJECTS

No vulnerable subjects will be included. Children, pregnant women, nursing home residents or other institutionalized persons, students, employees, prisoners, and persons with decisional incapacity will not be included in this study.

RECRUITMENT, ENROLLMENT, AND REMUNERATION

Recruitment of patients into the study will be done from clinics previous patients, referrals from other physicians, patient advocacy groups, direct website inquiries, and public outreach informational events.

1. Marketing:
   Marketing will be done primarily online via informational websites, patient outreach and advocacy groups.
2. Referrals:
   Recruitment of patients into the study will also be done via referral from physicians. No compensation will be given to referring physicians.
3. Patient fees:
   Patients will pay a fee for treatment that is within the normal range of comparative treatments worldwide. This will cover all costs including physicians and nursing staff, surgery center fees. Routine screening will be paid for by patient, however, no fees will be charged to the patient for additional images or tests directly related to the study.

POSSIBLE SIDE EFFECTS

Besides soreness from the fat harvest procedure, and at the site of injection, there have been very few adverse effects reported with autologous biologic therapies. Patients may experience aggravated stiffness and pain in the treated area.

ADVERSE EVENT REPORTING

Study sites will document all adverse reactions that occur (whether or not related to study drug or procedure) Significant adverse events will be reported to the IRB immediately.

FOLLOW UP AND REVIEW

At 24 hours, 1 week, 5 weeks, 3 month, 6 month, and 1 year intervals patients will be asked to participate in follow up protocols. Patients will not incur any and also be made available for the IRB to review.

PATIENT CONFIDENTIALITY

Patient names will be removed prior to submitting to any third party for review in order to maintain patient confidentiality.

WITHDRAWALS

Participation in the study is voluntary and patients may withdraw at any time. Patients who withdraw prematurely will not be replaced, but investigators will determine if it is in the best interest of the study to extend the study in order to obtain the desired number of subjects. An inquiry will be made as to the reason for termination and an assessment of the patient's wellbeing at the time. If the termination is the result of an adverse event this will be reported.

DATA COLLECTION, RETENTION AND MONITORING

Information from initial patient screening including demographic variables, data from follow up visits and self-administered questionnaires will be entered or uploaded into a comprehensive HIIPA compliant database.

SUBJECT CONFIDENTIALITY

In order to maintain confidentiality, only a subject number and initials will identify all study subjects entered into the database and on all documentation submitted to the Sponsor.

STATISTICAL METHODS

Patients who receive at least one follow up visit will be included in the analysis. Data for presentation and publication will be shared between investigator and sponsor.

END POINT

At both 6 months and 1 year assessments will be made with the patient to assess the above outcome measure and adverse effects from treatment. This will be evaluated along with the images and functional scores to evaluate clinical outcome. Patient tracking will continue for an additional 2 years.

INVESTIGATOR RESPONSIBILITYIES

The Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.

5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312

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