Clinical Outcomes of Hamstring ACL Reconstruction Augmented by an Injectable Osteoconductive/Osteoinductive Compound

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1) Protocol Title

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2) Objectives*

The goal of this study is to determine whether the use of injectable osteoinductinve/osteoconsuctive compounds (OOC) during ACL reconstructive surgery, combined with an accelerated rehabilitation protocol (ARP) provides clinical outcomes superior to those attained via traditional ACL reconstruction and delayed rehabilitation protocols.

3) Background*

Injury in anterior cruciate ligament (ACL) is common and often requires reconstructive surgery to restore normal stability to the knee [1]. The process of rehabilitation after ACL injury can last for several months or even years, and represents a significant psychological and economic burden for the athlete [2]. Although several surgical techniques are available for ACL reconstruction (see for instance [3, 4]) and many rehabilitation protocols have been implemented (see reviews [5-7]), there is no unanimous consensus on which types of operative procedure and rehabilitation routine can provide the shortest time of recuperation for the injured athlete.

Osteoconductive/osteoinductive compounds (OOC) are biomaterials characterized by bioactive properties: they provide an appropriate scaffold for bone formation (osteoconductivity); also, OOCs are able to bind and concentrate endogenous bone morphogenetic proteins in circulation, thus promoting osteogenesis (osteoinductivity) [8]. The faster ossification mediated by OOC injected in the bone tunnel could improve the structural stability of the graft construct, allowing the knee joint to adapt to bearing physiological mechanical loads sooner.

To test our research hypothesis we will perform a longitudinal analysis aimed at comparing clinical outcomes in athletes undergoing ACL reconstruction with injected OOC followed by either a delayed rehabilitation program (DRP) or ARP to that of athletes receiving a standard ACL reconstruction followed by either DRP or ARP. During the time frame of one year, tunnel expansion and graft-tunnel incorporation attained with the four different treatments administered will be periodically assessed via MRI scan.

If our central hypothesis is confirmed by the results of our analysis, we will have delineated a new treatment for ACL injury which can guarantee a faster postoperative recovery, thus reducing both the economic and psychological burden of the athlete.

4) Inclusion and Exclusion Criteria*

Inclusion criterion is any adult (male or female) undergoing a surgical procedure for hamstring ACL reconstruction.

Note: In this study, subjects belonging to the following populations will be **EXCLUDED**:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

5) Procedures Involved*

Surgical Procedures – Surgical procedures will be performed by Dr. Jan Pieter Hommen.

For all the surgical approaches investigated, 2 different graft options will be utilized including 1) the patients' own hamstrings tendons or an 2) allograft tendon. Following standard surgical practices, the graft will be anchored to the bones without using cortical fixation buttons. More specifically, a bone tunnel matching the diameter of the graft will be reamed in the femur and tibia. Subsequently, the graft will be passed and docked into the femoral and tibia tunnels with suspended fixation on the external cortices with Arthrex BTB Tightrope 12mm or 15mm metallic buttons (Arthrex, Naples, FL). In procedures involving the use of OOC, the bioactive compound (StimuBlast®, Arthrex, Naples, FL) will be mixed with 5cc of platelet rich plasma (PRP) harvested from the patient as per Arthrex protocol. Subsequently, the mixture will be injected using a syringe into both tibia and femoral tunnels prior to the docking of the graft within the femur and tibia tunnels. Note that mixing of StimuBlast® and autologous PPR is an FDA approved procedure which is highly recommended from Arthrex in order to get best results from the use of their OOC (see StimuBlast® brochure). In fact, it has been reported that PRP enhances bonw healing and regeneration [9].

Rehabilitation protocols – Delayed rehabilitation protocol consist in the use of a knee brace for the first 3 weeks after procedure, immediate closed chain and isometric kinematic strengthening with advancing weight-bearing exercises from partial to full weight bearing by 3 weeks postoperatively with the use of crutches until the gait normalizes. In contrast, accelerated rehabilitation protocols consist of: a knee brace for 3 weeks postoperatively utilized at night time only in full extension; crutches for three weeks until gait normalizes; closed chain and isometric kinematic exercises; open chain kinematics hamstring strengthening within a range of motion of 60 and 90 degrees.

Evaluation of clinical outcomes and biomechanical performance – In order to assess the effectiveness of the combination of the proposed surgical approach together with rehabilitation protocols, clinical, diagnostic and biomechanical relevant outcomes pertaining to the four subjects' groups investigated will be evaluated at several time points during the rehabilitation process.

Radiographic and Magnetic Resonance Imaging (MRI) – Radiographic tunnel measurements will be made at the initial post-operative evaluation followed by 3, 6, and 12 months postoperatively with digital PACS imaging, standardizing any potential image magnification. Bone tunnel measurements will be performed by board-certified orthopedic surgeon (Dr. Hommen) using digital measurements. Tunnel diameter sizes measured at the widest diameter for the femur and tibia will be compared to the size of the tunnels drilled at the time of surgery. MRI scan imaging will be performed at 3 months post-surgically. Grafts will be rated as 1) no signs of incorporation, 2) partial incorporation, 3) complete incorporation, 4) signs of tunnel cyst formation, 5) no evidence of tunnel cyst formation, 5) evidence of tunnel expansion, 6) no evidence of tunnel expansion 7) intact graft, 8) stretched graft, 9) evidence of graft failure. Alongside with these qualitative metrics, a quantitative image analysis will be performed to evaluate ACL reconstruction. More specifically, to quantify the normalized signal intensity of the ACL graft (related to ligament vascularization), the signal/noise quotient (SNQ) will be calculated using a region of interest (ROI) technique with the following equation:

SNQ = (signal of ACL graft - signal of quadriceps tendon)/signal of background

A custom-made image analysis software will be used for this analysis. The intra-articular signal of the ACL grafts will be divided into 3 zones to analyze the signal intensity. The distal (tibial), middle, and proximal (femoral) thirds will be defined as the first, second, and third zones, respectively. The signal from the tendon of the quadriceps femoris will be measured with the ROI in the patellar upper limit level to normalize the signal intensity of the ACL graft.

The MRI will be performed on a single MRI scan machine with the knee placed in the neutral position in an extremity coil. No contrast agent will be used. The coronal and sagittal images will be acquired using fast spin-echo (FSE) proton density–weighted imaging (PDWI), sagittal FSE T2-weighted imaging, and axial and ACL oblique fat-saturated FSE PDWI. The repetition time (TR) range and echo time (TE) values were variable (3000-4000/10-30 milliseconds for PDWI and 3000-5000/100 milliseconds for T2-weighted imaging). The other imaging parameters will be as follows: matrix, 220 3 247 (axial and coronal) and 304 3 301 (sagittal); field of view, 16 cm; slice thickness, 5 mm; and acquisition number.

Biomechanical outcomes - Aimed at evaluating patients' recovery after ACL injury, previous studies have investigated gait characteristics and lower limb muscular activation during walking and dynamic balance. Similar analyses will be performed

in this study. More specifically, gait characteristics during walking will be measured via lower limbs motion capturing analysis in combination with EMG analysis: kinematics, forces, moments, and power at each lower limb joint will be measured together with extent of muscular contraction of vastus medialis, vastus lateralis, bicep femoris, gluteus maximus, soleus and gastrocnemius. All the biomechanical experiments will be performed at the Biomechanics Research Lab of the University of Miami, under the supervision of Dr. Travascio (PI) and Dr. Asfour (co-PI) at 3 weeks, 3 months, 6 months and 12 months after surgery. Note that, in order to perform this biomechanical analysis, the already approved IRB protocol 20110778 (Motion Capture and Clinical Gait Analysis – PI: Dr. Asfour) will be used.

Statistical analysis – The question of interest is whether the uses of OOC will have any effect on bone tunnel expansion. We will have two groups:standard surgical procedure (control)and OOC-based surgical procedure (treatment). Each tunnel measurement will be treated as a paired observation (i.e., postoperative change of sclerotic margins of the bone tunnel compared with the initially drilled tunnel size). A 2-sample t-test will determine statistical significant differences between treatment and control.

A similar statistical approach will be followed for all the other clinical and biomechanical measurements performed in this study (i.e., quantitative image analysis of graft incorporation, lower joints kinetics, kinematics, and energetics, and activation of lower limb muscles) at the prescribed time points (i.e., at 3 weeks, 3 months, 6 months, and 12 months).

6) Data and Specimen Banking*

Data collected will include patients' post-operative MRI images, together with type of surgical procedure received and rehabilitation protocol.

The data collected will be anonymized and recorded in form of DICOM on a portable storage device by Dr. Hommen. Subsequently, either Dr. Hommen will personally deliver the storage device to Dr. Travascio (PI), who will transfer the data onto a remotely accessible computer located in Hungar Building at University of Miami (Coral Gables, FL). Only Dr. Travascio and the Co-Investigator (Dr. Asfour) will have the credentials for accessing the data, which will be stored for the duration of the entire study (estimated to be up to 5 years).

Access of data for immediate or future use will be only granted by the PI or the Co-Investigator to their staff members, provided that the intended use is within the scope of this study.

7) Data Management*

The question of interest is whether the uses of OOC will have any effect on bone tunnel expansion. We will have tunnel expansion measurements divided into two groups: standard surgical procedure (control)and OOC-based surgical procedure

(treatment).. Each tunnel measurement will be treated as a paired observation (i.e., postoperative change of sclerotic margins of the bone tunnel compared with the initially drilled tunnel size). A 2-samples t-test will determine statistical significant differences between treatment and control.

A similar statistical approach will be followed for all the other clinical measurements performed in this study.

From the location of data collection (Hommen Orthopedic Institute or Orthopaedic & Sports Medicine Center of Miami), data will be delivered to the Biomechanics Research Laboratory in an anonymized format. Data banking and access will be controlled by the PI (Dr. Travascio) and the Co-Investigator (Dr. Asfour) as described in section 6 'Data and Specimen Banking', see above.

8) Risks to Subjects*

OOC injection: Adverse effects specific to the use of StimuBlast® have not been reported. However, adverse events, such as inflammation or infection, have been reported in orthopaedic procedures which involved use of osteoconductive/osteoinductive compounds.

PRP extraction and administration: Minimal risks are associated with PRP extraction and administration. A bruise may form at the location where the blood sample is extracted. Risks (minimal) associated to its administration are no different from those associated with conventional cortisone injections.

MRI scan: There are some risks associated with MRI. For instance, patients with pacemaker cannot get an MRI. In addition, implanted medical devices that contain metal could not work well or heat up during the exam. Moreover, skin irritations or burn can occur in patients with tattoos or having medication patches. Finally, some patients may feel claustrophobic or scared of being in a very small space while getting the MRI done.

9) Potential Benefits to Subjects*

Possible benefits include a faster incorporation of the ACL graft into the knee if the injection of osteoconductive/osteoinductive compound is performed. This may lead to a faster post-operative recuperation of the function of the knee.

10) Vulnerable Populations*

This research does not involve individuals belonging to vulnerable populations.

11) Setting

Patients' medical images will be collected by Dr. Hommen's staff at Hommen Orthopedic Institute. Data collected will be analyzed at the Biomechanics Research Laboratory of the University of Miami, Coral Gables Campus, under the supervision of the PI (Dr. Travascio), and the Co-Investigator (Dr. Asfour).

12) Resources Available

Dr. Francesco Travascio (PI) is Assistant Professor at the Department of Industrial Engineering of University of Miami. He has a strong experimental and theoretical background in connective tissue biomechanics with specific training in biomedical image analysis and articular cartilage. As an R&D engineer in a company producing navigation systems for robot assisted orthopaedic surgery (MAKO Surgical Corp.), he developed novel techniques for radiographic image analysis to be used for intraoperative robot navigation. This acquired expertise will be fundamental for the medical image analysis planned in this study. As a PI for this study, Dr. Travascio will lead and supervise all the aspects of the data analysis.

Dr. Shihab Asfour (Co-Investigator) is Professor and Chair of the Department of Industrial Engineering and Associate dean of College of Engineering at the University of Miami. He has been working for more than 30 years in the field of musculoskeletal biomechanics, along with prevention and treatment of sports injuries. Dr. Asfour has an extensive knowledge on statistical data analysis. Accordingly, within the scope of this project, he will mainly provide support in the analysis and the interpretation data produced in this research.

Dr. Jan Pieter Hommen, M.D. (Surgeon/Co-Investigator) is the director of the Hommen Orthopaedic Institute. He is a surgeon specialized in comprehensive injuries and pain of the shoulder, hip, knee and ankle. The Hommen Orthopaedic Institute provides a unique scientific environment with a wealth of expertise with whom the PI will be able to consult at any time while carrying out the research proposed. In addition, within the scope of this study, Dr. Hommen will be in charge of performing surgical procedures on patients, and of providing clinical insights.

13) Prior Approvals

This research is currently supported by funds donated to the Biomechanics Research Laboratory. Also, we are currently applying for funding to Foundation for PM&R.

14) Recruitment Methods

Subjects will be recruited at any time during the next two years, also based on their availability.

Subjects will be recruited from both Dr. Hommen's existing patients.

Potential candidates as subjects for this study will be selected by Dr. Hommen according to matching criteria for this study (i.e., subjects must receive surgical treatment for ACL reconstruction).

No recruitment material will be used in this study.

There is no remuneration for participation in this study.

15) Local Number of Subjects

We estimate that, during the course of the duration of the project (up to 5 years, depending on funding resources), data form a total of 200 subjects will be collected.

16) Confidentiality

Data will be archived in a remotely accessible computer located Hungar Building of University of Miami (Coral Gables, FL). Only the PI (Dr. Travascio) and the Co-Investigator (Dr. Asfour) will have the credentials for accessing the data.

Data will be stored indefinitely.

Access of data for immediate or future use will be only granted by the PI or the Co-Investigator. Data access will be only granted to PI's staff members, provided that the intended use of the data is within the scope of this study.

17) Provisions to Protect the Privacy Interests of Subjects

We anticipate that there are no foreseeable conflicts of privacy for the individuals who participate in this study. Moreover, subjects' information will remain stored in

a password-protected computer, as described in detail in section 6 'Data and Specimen Banking'. Any personal information that could present a conflict to a subject's privacy will not be stored or published since archived data will be anonymized, see section 7 'Data Management' for details.

18) Consent Process

In order to participate to this study, subjects will have to sign a consent form (see HRP 502 – Consent Form - Travascio attached). In addition, they will be asked to complete a HIPAA Authorization form (see HIPAA Authorization Form attached). The signing of both consent form and HIPAA authorization will take place in presence of your othopaedic surgeons.

Only English-speaking subjects will participate in this study.

Only adults will participate in this study.

19) Process to Document Consent in Writing

Experimental research for this study presents no more than minimal risk of harm to subjects. In order to participate to this study, subjects are required sign a consent form and a HIPAA authorization form (see attached files).

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