Comparison of BioCartilage® versus Marrow Stimulating Procedure for Cartilage Defects of the Knee

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1. Background and Significance

Recent developments in the treatment of articular cartilage defects have resulted in several techniques that involve the stimulation of native cellular components for the purpose of differentiation and proliferation in the cartilage defect. Techniques of interest for this study are the use of microfracture combined with platelet rich plasma (PRP), and a recently developed augmentation of the microfracture procedure—BioCartilage®.

The microfracture procedure is performed with PowerPick™. During the procedure, a patient with focal cartilage defect undergoes arthroscopic debridement of the defect before microfracture is used to create holes in the subchondral plate in order to provide access to mesenchymal stem cells (MSCs). The procedure is complete at this point for patients undergoing a MSP without BioCartilage®.Other patients, who are undergoing a marrow stimulating procedure (MSP) with the BioCartilage® adjunct, will then have the microfractured region filled with PRP harvested intraoperatively from the patient, and a fibrin glue is then used to cover the defect and hold the PRP repair in place.

This basic MSP has been shown to regenerate cartilage tissue and improve joint function. Microfracture treatments using PRP are "shown to have good to excellent short-term outcomes in appropriately indicated patients" (Abrams, Mall, Fortier, Roller, & Cole, 2013), however successful long-term outcomes have not been demonstrated in the literature.

BioCartilage®, a novel therapy developed by Arthrex Inc, is implemented as an augmentation of the basic approach of using microfracture and PRP. All aspects of the procedure, as well as indications for the procedure, are the same as the basic MSP described above, except the PRP is combined with BioCartilage® powder, which acts as a scaffolding for cellular growth. BioCartilage® is an FDA approved augmentation of microfracture treatment with PRP, and the powder itself contains no living cells.

Animal models using BioCartilage® have provided data that supports the assertion that the BioCartilage® augmentation may improve outcomes for patients who receive it; however there is currently no published human clinical outcomes data available for using BioCartilage® (Abrams et al., 2013).

During the course of this study, we will gather and compare clinical outcomes data for patients who are receiving basic MSP for focal defects of the knee (trochlea or femoral condyle) to outcomes data for patients receiving the same MSP augmented with BioCartilage®.

There are no known benefits available exclusively to the subjects participating in this study. The only known risk for the subjects participating in this study include a slightly increased risk of injury associated with an MRI performed post-operatively.

2. Trial Objectives and Purpose

The rationale for conducting this study is to obtain clinical outcomes data on human subjects using BioCartilage® treatment for focal cartilage defects of the trochlea and the femoral condyle.

The null hypothesis: There is no significant difference between BioCartilage® and MSP in lesion tissue fill amount or quality based on MRI assessments.

The primary endpoint is to determine whether subjects receiving MSP augmented with BioCartilage® have improved outcomes (measured using quality of life indicators, functional outcomes, and MRI) compared to subjects who receive MSP without the use of BioCartilage®.

3. Selection of Subjects

The population to be studied will include individuals who are undergoing MSP with or without BioCartilage® treatment for focal defects of the knee (trochlea or femoral condyle). Up to 60 subjects will be enrolled in this study.

Sample size selection is based on pre-study statistical power analysis using data from an equine study in progress with arthroscopic scoring and histology grading of defect tissue amount and quality.

Subjects will be 18-years of age or greater, and be candidates for a procedure involving a MSP with microfracture and PRP, with or without BioCartilage® (or have already undergone such a procedure), for treatment of a focal defect of the knee (trochlea or femoral condyle). Subjects will be identified among the Missouri Orthopaedic Institute's clinical and surgical patient population by the investigators and study staff. Recruitment will be attempted after the subject is identified as a study candidate according to inclusion/exclusion criteria. Informed consent will either be obtained at a pre-operative visit, or it will be obtained post-operatively; in both instances informed consent will be obtained prior to obtaining baseline data.

Inclusion and Exclusion Criteria:

I. Inclusion in the study will be considered when all of the following conditions are met:
    a. The subject is a candidate for the use of a MSP with microfracture and PRP, with or without augmentation with BioCartilage® (or has already undergone such a

procedure), for treatment of a focal defect of the knee (trochlea or femoral condyle).
b. The subject is 18-years of age or greater
c. The subject is able and willing to consent to participate in the study
d. The subject is expected to be able to safely undergo MRI at the 1-year follow-up visit (no contraindications present, such as metal implants)
e. Infection or inflammatory arthropathy (such as rheumatoid arthritis) is absent in the operative knee

II. Exclusion from the study will be determined by any one of the following conditions being met:
a. The subject is undergoing bilateral knee surgery
b. The subject is unwilling, or unable to consent due to psychiatric condition or legal incompetence
c. The subject is either pregnant, or a prisoner

Subjects with concomitant pathology of the knee (e.g., meniscal tear, or anterior cruciate ligament damage) will not be excluded, but the investigator will note concomitant pathology in the intraoperative data collection instrument.

4. Study Procedure

Patients who undergo the standard of care (SOC) treatment MSP using microfracture and PRP, with or without augmentation with BioCartilage®, for focal defect of the knee (trochlea or femoral condyle) normally meet with their physician pre-operatively, return for the operative procedure, and then follow-up at approximately 6 weeks, 26 weeks, 52 weeks, and 104 weeks.

In the course of this study, investigators will enroll the patient either before or after they perform the SOC procedure (MSP with or without BioCartilage®), then they will schedule SOC follow-up visits, and data will be captured at each visit. At the 52 week follow-up visit, the patient will receive a MRI that is not SOC. The MRI procedure and interpretation will be paid for by the sponsor of this study, Arthrex Inc. All other care will be billed to the patient as part of SOC.

Patients who are enrolled (consented) after the SOC procedure has already been performed will be approached to discuss enrollment just prior to departure on the Operative Visit, after they have recovered from anesthesia. Study staff will approach the patient in their room, determine that the patient is alert and oriented, and then present the informed consent form for their review and consideration. Patients will be given as much time as they would like to consider enrollment in the study. Completion of study activities (surveys) normally performed during the Pre-Operative Visit will be attempted at that time, but may be collected by phone or in person at any SOC clinic visit prior to the 6-Week Follow-Up Visit.

The timeline of study activities is shown in Figure 1, below:

	Pre-Operative Visit	Operative Visit	6 wk (1.5m) Follow-Up
Timeline / Window	Up to 6 weeks prior to the operative procedure.	Day 0	Day 42 (Day 28 through 56)
Study Activities	• Informed Consent Form • HIPAA Authorization • SF-12 • Marx Activity Rating • KOOS • IKDC Subjective	• ICRS Knee Scoring System	• SF-12 • Marx Activity Rating • KOOS • IKDC Subjective • Return to work • Return to sport/ recreation

	26 wk (6m) Follow-Up	52 wk (1y) Follow-Up	104 wk (2y) Follow-Up
Timeline / Window	Day 182 (Day 168 through 196)	Day 364 (Day 336 through 392)	Day 728 (Day 700 through 756)
Study Activities	• SF-12 • Marx Activity Rating • KOOS • IKDC Subjective • Return to work • Return to sport/ recreation	• MRI • SF-12 • Marx Activity Rating • KOOS • IKDC Subjective • Return to work • Return to sport/ recreation	• SF-12 • Marx Activity Rating • KOOS • IKDC Subjective • Return to work • Return to sport/ recreation

*Figure 1: Timeline of Study Activities**

**Note: Study activities from the Pre-Operative Visit may be performed post-operatively during the Operative Visit*

In addition to the study activities listed above, if a subject enrolled in this study is having future knee surgery (same side or contralateral to the MSP with or without BioCartilage®), which is unrelated to the index procedure, the knee that had the index procedure may be arthroscopically viewed. The investigator may also perform knee joint aspirations if the patient is having complications with the knee related to the index procedure or if they are having surgery on either knee that is unrelated to the index procedure.

Enrollment of a total of 60 patients will occur across two arms of the study (trochlea and femoral condyle), each with two cohorts (MSP with and without BioCartilage®), shown in Figure 2, below:

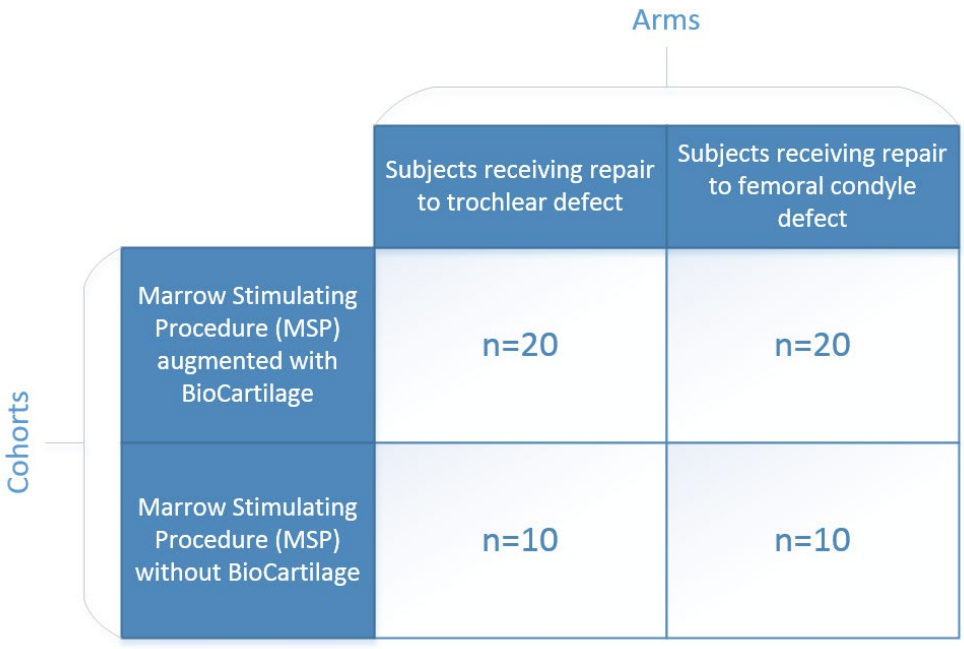

Figure 2: Cohorts and Arms

Assignment to a particular arm of the study will be determined by a subject's diagnosis (i.e., whether the defect is located at the trochlea or femoral condyle). Assignment to a particular cohort (MSP with or without BioCartilage®) will be based on the treatment decision that has been made by the investigator who is providing care to the patient in conjunction with the patient's wishes based on explanation of the study and treatment options.

The Informed Consent Form and HIPAA Authorization Form are modified standard forms provided by University of Missouri Health Sciences Institutional Review Board (IRB). The data collection instruments are as follows:

1. The SF-12® Health Survey
    a. Measures quality of life indicators
2. Marx Activity Rating Scale
    a. Measures activity type and level
3. The Knee Injury and Osteoarthritis Outcome Score (KOOS)
    a. Measures knee pain in relation to activity type in addition to qualitative description of knee pain
4. International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form
    a. Measures knee pain in relation to activity type
5. Return to work & sport/recreation (designed to assess whether subject has returned to their pre-injury level of work & sport/recreation.)
6. International Cartilage Repair Society Knee Scoring System

a. Intraoperative data for cartilage repair procedures, such as lesion size, definitive location of lesion, concomitant pathology, etc.

The Informed Consent Form and HIPAA Authorization Form will be printed on paper and all data collection instruments will be collected electronically using the OBERD system. In the event that the OBERD system is unavailable, comparable paper forms may be used in lieu of the OBERD data capture.

After data capture is complete, data will undergo statistical analysis.

5. Safety Assessment

Patients will be monitored post-operatively until discharge from inpatient care for signs and symptoms indicating that an adverse event has occurred. Signs and symptoms will be monitored and recorded by nursing staff according to institutional protocol. The investigator who is assigned to provide care for the subject will be responsible for review of nursing assessment information and to perform an interview and physical assessment before the patient is discharged to home.

After discharge from the operative visit, the investigator assigned to provide care to the patient will assess the patient at scheduled SOC follow-up visits. Any signs and symptoms indicating that an adverse event may have occurred will be communicated in writing via intra-organizational, secured email to the primary investigator (PI). The PI will determine whether an adverse event has occurred, and if so, this will be reported to the University of Missouri Health Sciences IRB in accordance with institution policy.

Adverse events and serious adverse events are defined below.
Adverse events:

I. Bleeding
II. Infection
III. Pain that is uncontrolled with standard post-operative analgesia protocol

Serious adverse events:

I. Bleeding that is significant enough to require extended hospitalization or unplanned critical care interventions
II. Infection that is significant enough to require extended hospitalization or unplanned critical care interventions
III. Pain that is significant enough to require extended hospitalization or unplanned critical care interventions

6. Tentative Timeline

We expect to fulfill the enrollment goal of this study (n=60) in two years or less, subject participation will last up to 110 weeks from the time of consent to last data capture, and data analysis is expected to be complete within 26 weeks of final data capture. Therefore, the study is expected to be completed in less than four years and 32 weeks.

7. Confidentiality of Data

Patient confidentiality during the course of this study will be protected in compliance with HIPAA requirements as well as the requirements of the University of Missouri Health-Sciences IRB.

After consent is obtained, all subjects will be assigned a study identification number that requires the use of a key in order to decipher a subject's personal identification information. The key will be kept in the Cerner Power Trials database, which is password protected. The study identification number will be used to label all paper data collection instruments.

All subject information in electronic format will be kept in password-protected storage. All subject information in paper format will be kept in locked cabinets in a secured suite at the Missouri Orthopedic Institute, and otherwise will be archived in a secure storage facility, or destroyed.

8. References

Abrams, G.D., Mall, N.A., Fortier, L.A., Roller, B. L., & Cole, B. J. (2013). BioCartilage: Background and Operative Technique. *Operative Techniques in Sports Medicine,* (21), pp. 116-24. http://dx.doi.org/10.1053/j.otsm..2013.03.008