

Study Title: Evaluation of the efficacy of radiofrequency-based debridement vs. mechanical debridement for the treatment of articular cartilage lesions.

NCT number: TBD

Date of Document: 02-Jul-2018

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1. STUDY OBJECTIVES

1.1 Study Purpose

The purpose of this study is to evaluate the changes in clinical and imaging outcomes following arthroscopic treatment of chondral lesion(s) by Radiofrequency-Based debridement or Mechanical Debridement in subjects 18-50 years of age.

1.2 Primary Objective

The primary objective is to evaluate the efficacy of Radiofrequency-Based debridement vs. Mechanical Debridement for the treatment of articular cartilage lesions.

1.3 Secondary Objective

The secondary objectives are to evaluate imaging and additional subjective and objective clinical outcomes.

2. STUDY ENDPOINTS

2.1 Primary Endpoint

The primary endpoint is to evaluate the change in Knee and Osteoarthritis Outcome Scores (KOOS) activity subscale at Week 52 post-operative compared to baseline

2.2 Secondary Endpoints

- Change in Visual Analogue Scale (VAS) scores from baseline
- Change in International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form scores from baseline
- Change in International Knee Documentation Committee (IKDC) Objective Knee Examination Form scores from baseline
- Change in Marx Activity Rating Scale from baseline
- Change in Work Productivity and Activity Impairment Questionnaire for Articular Cartilage Knee Injuries V2.0 (WPAI V2.0) from 1 week post-op to 6 weeks post-op
- Subject Satisfaction at Week 52 post-op

2.3 Imaging Endpoints

- ICRS grade of chondral lesion at Week 52 post-op
- MRI assessment at Week 52 post-op

3. BACKGROUND AND RATIONALE

3.1 Introduction

Knee chondral lesions are tremendously common. Chondral lesions documented in arthroscopies in the years 1989-2004 range from 59% to 63% (7). Outerbridge Grade 2 was the most frequent grade of the cartilage lesion at 42% (7). Arthroscopic chondroplasty allows removal of loose and damaged cartilage which minimizes synovial irritation and mechanical impingement (2). Two techniques for chondroplasty are radiofrequency (RF) and mechanical debridement (MD).

A 10-year randomized controlled study by Spahn et al., concluded that bipolar temperature controlled RF treatment at 50 degrees seemed superior to mechanical debridement in their short and medium term clinical outcomes and the progression of knee osteoarthritis (5). Subjects in the RF treatment group achieved a higher activity level 1 and 4 years after surgery compared to the MD treatment group (5). The time to required revision in the MD treatment group was 62.5 months with a rate of revision of 60.0% in comparison to 94.1 months and 23.3% in the RF treatment group (5).

A study by Lotto et al., showed thermal chondroplasty using radiofrequency energy (RFE) produced a larger depth of cellular death than mechanical debridement (MD) (3). Yet, RFE resulted in less healthy cartilage removal than MD (3). Lotto et al.'s results showed greater arthroscopic smoothing with less passes using RFE compared to MD (3).

Current safety concerns regarding RF treatment include the possibility that it contributes to the development of osteonecrosis. A prospective clinical trial by Turker et al., found no increase in the incidence of subchondral osteonecrosis with the addition of either mechanical or radiofrequency chondroplasty during arthroscopic meniscectomy (6). Similarly, of the 60 patients treated for grade III femoral chondral lesions by Barber and Iwasko (1), no osteonecrosis was observed at the 12 month postoperative MRI.

A systematic review by Papalia et al. concluded that RFE is efficient and safe for the surgical treatment of chondral lesions, specifically Outerbridge Grade 2 and 3 lesions (4). Grade 4 lesions were found to be too advanced to respond positively to debridement (4). The systematic review of past studies comparing RFE to MD found noticeable similarities to aims and design with a lack of randomization (4).

Additional randomized controlled studies are needed to prove that radiofrequency-based debridement is not inferior to mechanical debridement for the treatment of articular cartilage lesions. The primary objective of the proposed study is to evaluate the efficacy of RF debridement vs. MD for subjects requiring treatment of multiple chondral lesions in addition to a partial medial meniscectomy. Secondary objectives include evaluating imaging and additional subjective and objective clinical outcomes.

3.2 Study Device

The Smith and Nephew WEREWOLF COBLATION System is indicated for all soft tissue types in the knee. The WEREWOLF COBLATION System is a FDA cleared bipolar, radiofrequency electrosurgical system designed for use in orthopaedic/arthroscopic surgical procedures.

The WEREWOLF™ Controller and FLOW 50™ Wand obtained FDA 510(k) clearance (K162074) on August 22, 2016. Health Canada clearance is pending. The System consists of the following components:

1. A bipolar radiofrequency Controller with Integrated Fluid Outflow Regulator;
2. A non-sterile, reusable wired Foot Control and Power Cord
3. Sterile, disposable, single-use COBLATION Wands

3.3 Mechanism of Action

Smith & Nephew distributes COBLATION devices for ablation, resection, and coagulation of soft tissue and hemostasis of blood vessels in arthroscopic and orthopaedic procedures.

The FLOW 50 Wand is powered by the WEREWOLF Controller. This system uses a controlled radiofrequency-based plasma process (with the trademark 'COBLATION'). In this process, radiofrequency energy is used to excite the water molecules in a conductive medium, such as an electrolyte (saline) solution, to generate excited radicals within precisely focused plasma. The energized particles in the plasma have sufficient energy to break molecular bonds (16-18), excising or dissolving (i.e. ablating) soft tissue at relatively low temperatures (typically 40°C to 70°C). This technology is a radiofrequency-based technique but its mechanism of action is a chemical process and not a function of the radiofrequency energy itself.

The FLOW 50 Wand utilizes the Ambient™ feature which provides accurate ($\pm 3^\circ\text{C}$) real-time temperature monitoring of the intra-articular irrigating fluid.

These devices also provide the capability for hemostasis, typically delivered through devices that can also coagulate bleeding vessels.

4. PROCEDURES

4.1 Research Design

This is a non-inferiority, prospective, single blinded, randomized, single-center study design with enrollment of 82 randomized subjects (to assure 70 subjects complete the study). The sample size of 82 participants was calculated from a power analysis. The study was powered to detect at least a seven point change in KOOS pain score based on achieving 80% statistical power to detect a non-inferiority margin. Study duration will be until the last subject enrolled reaches 52 weeks post-operative.

The 82 randomized subjects will be randomized at a 1:1 ratio into the Werewolf Coblation wand treatment group or mechanical debridement treatment group. Subjects will be blinded to their treatment assignment until they complete all study visits. Upon withdraw from the study, termination from the study, or new or recurrent symptoms requiring a subsequent arthroscopy, the blinded assignment will be revealed to the subject.

4.2 Subject Recruitment and Screening

Subjects will be voluntarily recruited from the Principal Investigator or Sub-Investigator population and/or referring physicians.

Subjects will be screened to determine if they meet all inclusion and no exclusion criteria. If all entry criteria are accomplished, the subject will be eligible to participate in the study.

Eligible subjects will be provided an IRB approved Informed Consent Form for review and signature. Each subject will have a physical assessment by the surgeon and will complete all patient reported outcomes (KOOS, VAS, IKDC subjective, Marx). X-rays and MRI will be attained if previous imaging is greater than 3 months old.

All potential subjects screened for eligibility will be listed on the electronic Screening and Enrollment Log. The electronic Screening and Enrollment Log will document the date of screening, the results of screening, and the primary reason for excluding the subject. The electronic Screening and Enrollment Log will be kept on the research shared drive (encrypted and located behind the OSUMC firewall). The log will be password protected.

4.3 Study Duration and Follow-Up

Study duration will be until the last subject enrolled reaches 52 weeks post-operative.

Subjects will be assessed pre-operatively and return post-operatively at Day 10, Weeks 6, 24, and 52. At follow-up visit Week 24, the subject questionnaires will be administered online through RedCap. At follow-up visits Week 6 and 52, the subject questionnaires will be administered in the office. At each follow up visit, AEs and concomitant medication will be reviewed, as applicable. At week 52 post-operatively, the subjects will complete a MRI of the treated knee.

4.4 Measurement/Instrumentation

The change in the KOOS activity subscale will be the primary study endpoint. Secondary outcomes include time to return to work/activity and time to return to no pain. Baseline MRI will be compared to MRI at 52 weeks to evaluate knee morphology, cartilage signal, osteophytes, bone marrow edema, subarticular cysts, effusions and loose bodies. The international cartilage repair score will be used.

4.5 Detailed Study Visits

Screening

- Confirm written informed consent prior to screening procedures
- Inclusion/exclusion criteria
- Physical assessment by surgeon – IKDC objective
- Demographics
- Medical and surgical history

- X-rays unless provided (must be less than 3 months old)
- MRI unless provided (must be less than 3 months old)
- Patient reported outcomes
 - KOOS, VAS, IKDC subjective, Marx

Date of surgery

- Arthroscopic inclusion/exclusion criteria
 - No articular cartilage lesion present that requires treatment
 - Evidence of previous chondral treatment not noted at screening
 - Chondrocalcinosi
- Randomization
- Surgery performed

10 days (7 days-14 days post op)

- Explanation of the weekly online data to be collected on RedCap
 - KOOS activity, VAS, return to work/activity (WPAI V2.0). [To be completed weekly from 1 week post op to 6 post op]
- Physical assessment by surgeon – IKDC objective
- Patient reported outcomes
 - KOOS, VAS, IKDC subjective, Marx

6 weeks (\pm 5 days)

- Physical assessment by surgeon – IKDC objective
- Patient reported outcomes
 - KOOS, VAS, IKDC subjective, Marx

6 months (\pm 14 days)- To be completed in RedCap

- Patient reported outcomes
 - KOOS, VAS, IKDC subjective, Marx

12 months (\pm 28 days)

- Physical assessment by surgeon – IKDC objective
- Patient reported outcomes
 - KOOS, VAS, IKDC subjective, Marx
- X-rays (merchant view, AP and PA Rosenberg)
- MRI

4.6 Data Analysis and Study Validity

We will minimize selection bias by including a consecutive series of eligible cases until the sample size is achieved. Data will be analyzed using standard statistical software, STATA 13 (College Station, Tx). Descriptive statistics will be generated for the total sample. We will assess the difference in our primary and secondary outcomes.

5 SELECTION OF SUBJECTS

Subjects who meet all of the following criteria will be voluntarily recruited by participating Investigators:

5.3 Inclusion Criteria

Subjects MUST meet ALL of the following criteria to be included in the study:

- Given written informed consent on the IRB approved consent form specific to the study, prior to study participation
- 18-50 years old
- Male or Female
- Suspected chondral damage in the following locations where debridement is indicated:
 - Medial femoral condyle
 - Lateral femoral condyle
 - Trochlea
 - Patella
- < 30% joint space narrowing as seen on x-ray (merchant view, AP and PA Rosenberg)
- 1 or more chondral lesion(s) as noted on MRI
- Concomitant procedures are allowed unless noted in the exclusion criteria

5.4 Exclusion Criteria:

- Previous chondral treatment in the same compartment (prior debridement and lavage performed more than *three* months prior to baseline are acceptable)
- Focal chondral defect indicated for concomitant procedures (i.e., microfracture, ACI, MACI, OATs)
- Concomitant procedures that are not allowed:
 - Lateral retinacular release
 - Excision of osteophytes
 - Subchondroplasty
 - Manipulation under anesthesia
 - ACL reconstruction
 - Quad tendon repair
 - Patellar tendon repair
 - Patellar tendon debridement
 - Multiligament reconstruction
- Pregnant and/or intending to become pregnant during this study period

6 REFERENCES

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