Study Title: A randomized controlled trial to compare single portal versus two portal knee arthroscopy techniques in patients with meniscal injuries and articular cartilage pathology

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Study Title: A randomized controlled trial to compare single portal versus two portal knee arthroscopy techniques in patients with meniscal injuries and articular cartilage pathology

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Background, Rationale and Context

Knee arthroscopy procedures provide a minimally invasive method to assess the status of the knee joint in order to repair injuries of the meniscus and articular cartilage. In the past, two or more small openings in the skin (portals) were required in order to allow the passage of both an arthroscope to provide visualization of the knee joint and the instrument used to complete the surgical repair process. However, recent innovations in arthroscopy instrumentation have resulted in the ability to use one portal for knee arthroscopy procedures with both the arthroscope and the instruments passed into the knee joint through the same portal. Both uniportal and two portal arthroscopic techniques are used currently for knee arthroscopy procedures in the Department of Orthopaedic Surgery at Wake Forest Baptist Health.

Objectives

This randomized, controlled clinical trial will compare the outcomes of single portal versus two portal techniques in patients who have meniscus or articular cartilage pathology. The study hypothesis is that patients who undergo single portal arthroscopy will have less pain post-operatively, use less pain medication, and have a higher International Knee Documentation Committee (IKDC) score at six months and one year compared to patients who undergo traditional two portal knee arthroscopy.

Methods and Measures

Design: A randomized, controlled trial

Setting: Academic Medical Center: single study site at Wake Forest Baptist Health

Subjects selection criteria

Inclusion Criteria

- Men and women between 21 and 65 years of age, who agree to comply with the protocol
- Patients undergoing a primary knee arthroscopy procedure for meniscus or articular cartilage pathology

Exclusion Criteria

- Patients with a history of long term pain medication use and/or chronic pain conditions unrelated to the surgery.
- Subjects with severe renal disease, allergies to pain medication, and subjects that will have adverse drug-drug reactions from prescribed pain medication.
- Patients with previous reconstructive procedures, lateral retinacular release, or microfracture
- Active knee infection or sepsis at the time of surgery
- Meniscal injuries requiring repair
- Ligamentous instability
- Advanced degenerative or inflammatory arthritis
- Known cancer at the time of surgery
- Conditions that might interfere with recovery from knee arthroscopy (i.e. conditions or diseases of the nervous and/or muscular system, vascular disease, uncontrolled diabetes)
- Malignant tumor history or treatment of malignant tumor of the knee
- Lower extremity condition causing abnormal ambulation (e.g. ankle fusion, ankle arthroplasty, previous hip fracture, knee arthrofibrosis)
- Pregnant, breast feeding, or planning on becoming pregnant during the time frame of the study, (if a woman of child-bearing age)
- Emotional or neurological conditions that affect the subject's ability or willingness to participate in the study including mental illness or drug and/or alcohol abuse
- Severely overweight (BMI >40) at study enrollment or surgery
- Currently participating in another research study
- Prisoner or impending imprisonment
- Workers' Compensation claims

Sample Size:

Power calculations were performed based on data from previous studies. Van de Graaf found a standard error of the mean (SEM) of 5.3 and a smallest detectable difference (SDD) of 14.6 for the Subjective Knee Evaluation Form part of the International Knee Documentation Committee (IKDC).(2) These measures were slightly larger than the SEM of 4.6 and the SDD of 9.0 reported by Irrgang.(1) Based on these values, power calculations identified the desired sample size as 50 patients in each surgical group to yield 84.7% power to detect a difference with an alpha = 0.05. In order to account for 10% missing data due to patient drop-outs and/or loss to follow-up, a total of 110 patients will be randomized and enrolled with 55 patients in each of the two surgical groups. The blocked randomization scheme will be designed for the potential enrollment of 60 patients in each of the two study groups.

Interventions and Interactions

Evaluation Schedule Summary:

Evaluation	*History / Pre-Op*	*Intra-Op*	*1 day*	*4 days*	*1 week*	*30 days ± 7 days*	*3 months ± 2 weeks*	*6 months ± 2 weeks*	*1 year ± 1 month*
Patient ● IKDC demographics	X								
● IKDC current health	X							X	X
● IKDC subjective knee evaluation	X					X	X	X	X
Patient phone calls ● Pain scores/pain medication log			X	X					
Physician ● IKDC knee history	X								
● IKDC surgical documentation form		X							
● IKDC knee examination form	X					X	X	X	X
• Document rehab duration						X	X		
Stitch Removal/ Postop Follow-up for Pain/Meds					X				

The study will include six visits: one pre-surgery visit and five post-surgery visits at one week, 30 days, three months, six months, and one year. The one week, 30 day, and three month follow-up visits coincide with the standard of care follow-up visits for patients who undergo knee arthroscopy. The six month and one year visits will be for research purposes and will not be billed to insurance providers.

Additionally, the patients will be contacted by phone at 1and 4 days after surgery to determine their visual analog pain scores and their use of pain medications. Patients will also keep a daily log of their pain level and use of pain medications. These calls will also be used to remind patients to complete their pain diaries.

Randomization: A blocked randomization scheme (block size of 10) will be used to assign study participants to either single portal (Group 1) or two portals (Group 2) knee arthroscopy. Prior to surgery, the surgeon will log on to the randomization website to determine each participant's surgical group assignment. After randomization for each patient is complete, the website will document the name of the person who logged on to perform the randomization, the date and time of the log in, and the surgical group assignment for each patient. In addition, the website will document the patient's name, medical record number, and study treatment allocation. This randomization information will be forwarded to the operating room staff so that they can prepare for each study participant's surgical procedure.

If during the surgical procedure, a patient who was randomized to the single portal technique is found to require a two portal technique, this patient will be recorded as a treatment cross-over as long as the patient continues to meet inclusion criteria. This will also be true for patients randomized to the two portal technique who undergo the single portal technique. Cross-over patients will not be excluded from the study. We are anticipating that only a small number of patients will be cross-over patients.

Surgery: Patients in Group 1 will undergo knee arthroscopy using a single portal. Patients in Group 2 will undergo knee arthroscopy using two portals. The details of the surgical procedure for each study participant will be documented on the IKDC Surgical Documentation Form.

Post-surgical follow-up: Study participants in each group will return for standard post-operative follow-up visits at one week, 30 days, and three months. They will return to the clinic at six months and one year for study visits. These two visits will not be billed to insurance providers.

Outcome Measures

Patient assessments:

Patients will complete the patient-related IKDC questionnaires at each study visit except the one week visit. The IKDC is used to monitor knee symptoms, function, and activity level (1) The IKDC was developed and revised by knee experts as a knee-specific rather than a disease-specific evaluation. (1) A recent study by Van de Graff, et al demonstrated that the IKDC was better in all its measurement properties than the KOOS or the WOMAC for evaluating patients with meniscal injuries. (2)

At the pre-surgery visit, study participants will complete several components of the IKDC questionnaires including the demographic form, current health assessment form, and the subjective knee evaluation form. Patients will maintain a daily log to document their use of pain medications for the first two weeks after surgery. In addition, study participants will complete the subjective knee evaluation form at one month, three months, six months, and one year.

Patients will be contacted by phone on post-surgical days 1 and 4 to remind them to complete their daily log and to report their pain level and medication use. At each phone call and clinic visit, patients will be asked two questions: *1. What day did you feel that you had completed recovering from the surgery?* and *2. What day did you stop taking pain medicine?* Patients also will be asked these questions at the 30 day clinic visit.

If patients are unable or decline to return to clinic for follow-up, we will try to collect the patient-completed questionnaires either by telephone, by mail, or by a web-based link sent to them via a REDCap database survey at any study time point.

Physician assessments:

The principal investigator will complete the IKDC knee history form, surgical documentation form and knee examination form at baseline. At 30 days, three months, six months, and one year the physician assistant or other designee will complete the knee examination form. Additionally, the rehabilitation duration will be noted at the 30 days and three month visit per patient report.

Patient Retention

Every effort will be made to retain patients in the study to ensure complete data collection. During the study consent process, potential study participants will be educated regarding the importance of full participation in all visits. Study participants will be called at 1 day and 4 days after surgery. At these calls, patients also will be reminded of their upcoming appointments. Patients will also be reminded about their follow-up visits at all clinic visits. Patients will also be given an information packet about the study. This packet will include a list of the dates for the phone calls and the dates of their follow-up clinic visits.

If patients are unable or decline to return to clinic for follow-up, we will try to collect the patient-completed questionnaires either by telephone, by mail, or a web-based link sent to them via a REDCap database survey at any study time point.

Analytical Plan

Primary outcome: The IKDC Subjective Knee Evaluation Form score will be the primary outcome measure. The IKDC subjective knee form contains 19 questions and requires approximately five minutes to complete.(2) All except one of the items is converted to a score; a

maximum score of 100 indicates that the patient has no restrictions in their daily activities or sports and does not have any knee symptoms.(2)

Secondary outcome: Pain levels and the use of pain medication will be monitored by study participants using a daily pain diary. The pain diary will be used for the first two weeks after surgery. Pain levels will also be collected at the 1 and 4 day telephone calls. A pain rating will also be collected at the one week, 30 day, three months, six months, and one year visit.

Data management: All study data will be entered into a REDCap database. The database will be HIPAA compliant and will meet all the requirements of the NIH and FDA. The REDCap server is behind a firewall and is backed up every 24 hours. The data will be sent as an Excel spreadsheet for analysis to biostatisticians in the Section on Biostatistics of the Department of Public Health Sciences at Wake Forest School of Medicine.

Human Subjects Protection

All patients with a diagnosis of meniscal or appropriate articular cartilage injury will be screened for inclusion into the study.

This study will be conducted in accordance with the current IRB-approved clinical protocol; ICH GCP Guidelines adopted by the FDA; relevant policies, requirements, and regulations of the clinical test site IRB; and applicable federal agencies.

Subjects may withdraw from the study at any time for any reason at their request. Otherwise, participants will be followed as per the protocol. Attempts will be made to collect clinical data from withdrawn subjects. There will be no replacement of subjects who withdraw from the study.

Subject Recruitment Methods

The study will recruit patients who present to the Orthopaedic Sports Medicine Clinic at Wake Forest Baptist Health with symptoms requiring arthroscopic knee surgery for meniscal or articular cartilage pathology.

Study screening and enrollment: Potential study participants will be screened in the Orthopaedic Sports Medicine Clinic. Patients with meniscus injuries who meet the study inclusion criteria will be told about the study and will be asked if they would like to participate. The study will be described, and the requirements for study participation will be explained. Potential study participants will be encouraged to ask questions about the study and to find out what is involved in study participation. A patient information sheet will be provided to the potential subject to explain the study and used as a recruitment tool. Patients who agree to

participate will be asked to provide informed consent. No study related procedures will occur until after the informed consent is obtained. Following completion of informed consent, the study participants will be asked to complete three of the six IKDC forms including questionnaires to document demographics, current health, and subjective knee evaluations.

Informed Consent

Signed informed consent will be obtained from each subject in the privacy of a clinical examination room. The study coordinator will discuss the study with patients who meet study entry criteria and will obtain consent while the patients are in the clinic following their visit with the surgeon.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, stored separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection, subject identifying information will be destroyed six years after closure of the study by shredding the paper documents and deleting the information from the computer files, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and Stryker Endoscopy, or appropriate government agency if appropriate.

Update to the study protocol:

The study sponsor, Stryker, Inc. has made a business decision to no longer fund or support the continuation of the study. The study team is unaware of any serious adverse events or

unanticipated risks to patients during the course of the study. Study participants will be offered a final close-out clinical examination visit of their study knee if they have not completed the study visits. This final research visit will be at no-charge to the patient or to their insurance company.

This final study visit will consist of a brief knee exam by a member of the study team and we will measure how well the patient can bend and straighten their knee (their range of motion). We would also ask the patient to answer a short survey about their knee function and pain. This survey is the same questionnaire the patient would have completed during the study at their regular study follow-up visits (the IKDC Knee Examination Form and IKDC Current Health Assessment Form). We anticipate this visit will take approximately 15-20 minutes. We still offer patient compensation of $10 for completion of this final study visit.

If the patient is having any other issues with their study knee, with their knee on the other side, or any other orthopaedic problems and would like to see an orthopaedic surgeon, we will offer to schedule an appointment for the patient as a regular clinical visit. However, the patient and/or their insurance provider will be charged for this appointment.

If the patient chooses not to return to the clinic for the knee exam, we will ask them to complete the final brief survey about their knee function and pain. This survey may be completed either on the telephone or by email through an electronic survey. If the patient declines to participate in this final knee exam and/or survey, we will note their decision and not contact the patient any further about this study.

Patients will be transferred to clinical management of their knee and they will be followed as part of standard clinical care by their orthopaedic surgeon in the future.

References

(1) Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 2001 Sep;29(5):600-13.
(2) van de Graaf V, Wolterbeek N, Scholtes VA, Mutsaerts EL, Poolman RW. Reliability and Validity of the IKDC, KOOS, and WOMAC for Patients With Meniscal Injuries. Am J Sports Med 2014 Mar 11.
(3) Cooper DE, Fouts B. Single-portal arthroscopy: report of a new technique. Arthrosc Tech 2013;2(3):e265-e269.
(4) Crawford K, Briggs KK, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the IKDC score for meniscus injuries of the knee. Arthroscopy 2007 Aug;23(8):839-44.

Appendix

1. International Knee Documentation Committee questionnaires
   - Patient Questionnaires
   - Physician Questionnaires

2. Pain logs