A Randomized Clinical Trial of Static versus Articulating Antibiotic Spacer for Treatment of Periprosthetic Joint Infection in Total Knee Arthroplasty

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A Randomized Clinical Trial of Static versus Articulating Antibiotic Spacer for Treatment of Periprosthetic Joint Infection in Total Knee Arthroplasty

Michael J Taunton, MD -- Principal Investigator
Matthew P. Abdel, MD, -Co-Investigator

Tad M. Mabry, MD – Co- Investigator
Arlen D. Hanssen, MD – Co- Investigator
Kevin I. Perry, MD – Co-Investigator

Abstract

Choice of treatment for periprosthetic joint infection for total knee arthroplasty has provided significant controversy in the orthopedic literature. A prospective randomized clinical trial is proposed to compare directly compare a randomized cohort of patients treated at a single institution by a single group of surgeons with expertise in the management of the infected total knee replacement. This study is designed to address the major clinically important issues between the two types of procedures with emphasis on functional outcome and survivorship free of infection. Patients will be randomized to receive resection knee arthroplasty with either a static or an articulating antibiotic spacer, followed by reimplantation total knee arthroplasty. Twenty-Eight cases will be assigned to each arm of the study (10% drop out rate) for a total of 50 cases to complete the trial.

The principal outcome measures include early functional outcome as assessed by the Mayo Knee Sheet, and SF-12 score. In-hospital and perioperative complications such as mortality, deep vein thrombosis, pulmonary embolus, neurovascular complications, and infection will be recorded. Satisfaction with surgery will also be assessed. Survivorship techniques will be used to evaluate time-to-event outcomes such as the need for revision surgery.

Potential impact of study results

To our knowledge, there is no published prospective randomized trial that critically compares the results of treatment of infected total knee arthroplasty with static and articulating antibiotic spacers. Currently, there remains only personal bias for choosing one surgical procedure over another. Both procedures are widely accepted and performed in the medical community. The findings from this work will be treated as valuable information to guide clinical practice.

Specific Aims

Choice of treatment for periprosthetic joint infection for total knee arthroplasty has provided significant controversy in the orthopedic literature. The purpose of this study would be to directly compare the results of a randomized cohort of patients treated with either with static or articulating antibiotic spacers. This will be performed at a single institution by a single group of surgeons with expertise in the management of the infected total knee replacement.

We hope to shed some light on the actual benefits of one procedure over the other. The remainder of the treatment of the knee infection in both approaches will be the same utilizing standard clinical practice for treatment of PJI in order to make both groups comparable with respect to outcome.

Background

Deep infection following total knee replacement presents a relatively rare, but devastating complication. The risk for deep infection hovers around 2 percent for a primary total knee replacement and increases in the setting of revision surgery. As the

number of total knee replacements performed annually continues to rise exponentially, the burden of treatment for the infected total knee replacement will rise accordingly.

It is important to consider not only the burden of treatment that applies to the patient, but also to the health care system. Managing the patient with an infected total knee replacement consumes an inordinate amount of healthcare resources. It is also a substantial cause of lost work and potential institutionalization during the treatment phase. For these reasons it will become more important over time that we establish the best possible treatments for the infected total knee replacement.

The infected total knee replacement is categorized by the timing of the infection. This will typically guide treatment.

Acute infections, including infections that occur in the first three or four weeks postoperatively (acute postoperative infection) and infections in the setting of bacteremia with a short duration of symptoms (acute hematogenous infection) are often treated with irrigation and debridement with component retention. Following surgery, these patients are treated with a course of IV antibiotics followed by a prolonged course of oral antibiotics.

In the setting of a more chronic infection the gold standard for treatment in the United States is a two-stage exchange. The first stage is characterized by resection of all components, foreign material and necrotic tissue. At the time of the first stage it is typical practice to place some type of high dose antibiotic cement spacer. The high-dose antibiotic-loaded cement spacer has shown to be clinically safe[1] In general terms, the purpose of the spacer is to stabilize the soft-tissue envelope in order to facilitate later

reimplantation. It is also a mechanism for the delivery of high-dose local antibiotics into the infected field.

There are two basic types of spacers that can be placed at the time of the first stage resection. These are the static antibiotic spacer and the articulating antibiotic spacer. Utilizing a static spacer in a two-stage exchange protocol for infected total knee arthroplasty, Haleem, et al[2] found survivorship free of implant removal for any reason was 90% at 5 years and 77.3% at 10 years. The survivorship free of implant removal for reinfection was 93.5% at 5 years and 85% at 10 years. These results suggest that the high likelihood of early success after two-stage reimplantation with a static spacer is maintained throughout long-term follow-up, with a modest rate of late recurrent infection or mechanical implant failure.

A study by Fehring et al[3] retrospectively reviewed 25 patients treated with static nonarticulating spacers and 30 patient with articulating spacers. Survivorship of the static spacer was 88% at 36 months f/u. The survivorship of the articulating spacers at 27 months was 93%. The average Hospital for Special Surgery score was 83 points in the patients with static spacers and 84 points for the patients with articulating spacers. Range of motion, at final follow-up, was an average of 98 degrees in the patients who received static spacers and 105degrees in the patients who received articulating spacers. Similarly, Chiang, et al[4] found similar results with equivalent rates of eradication of infection in both groups. They did find superior satisfaction in the articulating group (21/23) vs 7/23 in the static group.

There has never been a randomized, head-to-head comparison of these two types of spacers. Prior studies have been retrospective analyses. Both studies by Fehring, et al [3]and Chiang et al[4]were retrospective series when techniques were evolving. There was no classification of bone loss, or consideration of severity of infection or bone loss between the cases, making it difficult to make any real conclusions on both eradication of infection, and postoperative function. Assessments of "satisfaction" and range of motion in non-comparable groups gives little guidance for treatment.

Hypotheses

1. The 1-year post-operative range of motion and Knee Society score will be superior after reimplantation Total Knee Arthroplasty performed after articulating spacer than TKA reimplantation after a static spacer.
2. Patient satisfaction is higher after articulating cement spacer when compared to static cement spacers.
3. The rate of repeat infection after reimplantation Total Knee Arthroplasty performed after articulating spacer will be equal to TKA reimplantation after a static spacer.
4. The survivorship of Total Knee Arthroplasty (TKA) reimplantation performed after articulating spacer will be equal to TKA remplantation after a static spacer.

Materials and Methods

<u>Basic Study Plan</u>

A prospective randomized clinical trial is proposed to compare the results of treatment of infected total knee arthroplasty with static or articulating antibiotic spacers. This study is designed to address the major short-term clinically important issues between the two types of procedures with special emphasis on survivorship and clinical outcomes. A research coordinator will supervise the running of the study. The patient and the surgeon will not be blinded to the operation performed.

Surgical Technique

All procedures will be performed by the principle investigators (TMM, ADH, MJT, MPA, KIP) with a subspecialty interest in total knee arthroplasty. All bone loss will be classified both for the femur and tibia, and recorded in the operative report.

Resection Total Knee Arthroplasty with placement of static Antibiotic Spacer

The technique for use of the static spacer would include complete resection and debridement at the time of initial resection. The antibiotic cement would contain 3 grams of Vancomycin and 3 grams of Gentamicin per 40 gram batch of cement. The technique would involve the creation of two intramedullary antibiotic cement dowels followed by capping the distal femur and proximal tibia in a standardized fashion. The remaining space in the tibiofemoral joint would be filled with antibiotic cement in a standard technique. The leg would be casted, at least until the time of wound healing. After the first cast change and suture removal the leg could be placed into a cast or knee immobilizer at the surgeon's discretion. The weightbearing would be allowed 40 to 60 pounds of weight (partial weightbearing). When feasible, the patient would receive erythropoietin between stages where possible. The patients would be screened and decolonized for colonization with staphylococcus aureus as indicated. The patients

would receive six weeks of organism-specific antibiotics in coordination with Orthopedic Infectious Disease. The patients should be scheduled for reimplantation between 8 and 12 weeks following knee resection. The final decision regarding reimplantation versus repeat debridement and spacer exchange would be based on the surgeon's evaluation of the soft tissues, laboratory studies, radiographs and intraoperative evaluation at the time of planned reimplantation which would include both the gross and microscopic appearance of the peri-articular tissues.

Resection Total Knee Arthroplasty with placement of articulating Antibiotic Spacer.

The technique with the articulating antibiotic cement spacer would be very similar. The main difference would be, instead of filling the tibiofemoral space with a static spacer, we would utilize a modular posterior stabilized femoral component and a modular polyethylene liner. We would utilize a standard technique for the placement of this articulating spacer, which would include high-dose antibiotic cement of the femoral component into an appropriate position as well as modifying the counter surface of the modular posterior stabilized liner for cementation. As in the static spacer technique, the limb would be placed into a cast or knee immobilizer full time until wound healing. The patient would be allowed partial weight bearing. However, in contrast to the static spacer protocol, once the wound has been found to heal in a satisfactory fashion, the patient would perform self-directed physical therapy to include quad sets and active range of motion two to three times daily within the range of comfort. The patient would be instructed to wear the immobilizer or other type of knee orthosis locked in extension when not performing the active range of motion exercises. The remainder would be the same between techniques.

Hospitalization

Patients will come into the hospital on the day of their surgery, unless medical problems dictate earlier admission. Hospitalization of 3 nights is routine for these patients, although complications may prolong that time. The patient will receive one preoperative dose of antibiotics if the organism is known preoperatively Antibiotics are typically held preoperatively if infection is highly suspected, but no organism has been identified by prior pre-operative studies. All patients will receive appropriate antibiotics postoperatively which will be tailored to the infection. All patients will receive appropriate anticoagulation for deep venous thrombosis prophylaxis.

Postop Physical Therapy

Both treatment groups will have similar postoperative care. Structured physical therapy will begin the day after surgery and continued during the hospitalization. Patients are encouraged to sit up at the bedside the evening of their surgery. A home therapy program will be given to the patient although formal physical therapy will not continue on an outpatient basis.

a. Post-op Day 1, use of walker or personnel to assist with transfer from bed to chair.

b. No Range of motion in the affected knee.

c. Weight bearing status 40-60 lbs.

Progression

- Progress ambulation utilizing walker to crutches.

- Patients should be encouraged to maximize independent ambulation and increase distance ambulated daily under the above listed restrictions.

Discharge Criteria (home going)

- Independent and safe with aids
- Transfer out of and into bed from a standing position
- Rise to and from a chair to a standing position
- Ambulate 100 feet

Study Procedures Summary

Data Collection (obtained via the research assistant and prospectively entered into a computerized data base (RedCap))

Visit #1 Preoperative: Aspiration of knee (Send synovial fluid for cell count, culture). Labs: Erythrocyte sedimentation Rate, C-Reactive Protein, Complete Blood Count with differential. Consent.

Visit #2 Preoperative: Radiographs of the knee, Mayo Knee Sheet, SF-12 Version 1, measurement of clinical parameters, Range of motion, Knee Society Score: Pre-Op.

Operative #1: Radiographs of the knee, complications. Classification of bone loss.

Visit #3 Two Weeks: Mayo Knee Sheet, SF-12 Version 1, measurement of clinical parameters, Wound Examination, Knee Society Score: Post-Op.

Visit #4 Preoperative 2nd Stage (typically 8 weeks) Mayo Knee Sheet, SF-12 Version 1, measurement of clinical parameters, Wound Examination. Range of motion for articulating group. Knee Society Score: Post-Op . Labs: Erythrocyte sedimentation Rate, C-Reactive Protein, Complete Blood Count with differential.

Operative #2: Radiographs of the knee, complications.

Visit #5 Two Weeks: Mayo Knee Sheet, SF-12 Version 1, measurement of clinical parameters, Wound Examination. Range of motion (both groups). Knee Society Score: Post-Op.

Visit #6 Two Months: Mayo Knee Sheet, SF-12 Version 1, measurement of clinical parameters, Wound Examination. Range of motion (both groups). Knee Society Score: Post-Op Labs: Erythrocyte sedimentation Rate, C-Reactive Protein, Complete Blood Count with differential.

Visit #7 One Year: Mayo Knee Sheet, SF-12 Version 1, measurement of clinical parameters, Wound Examination. Range of motion (both groups). Knee Society Score: Post-Op. Labs: Erythrocyte sedimentation Rate, C-Reactive Protein, Complete Blood Count with differential.

	Preop visit #1	Preop visit #2 (Listing)	Operative #1	Postop 2 week (#3)	Pre-op Stage 2 (#4)	Operative #2	Postop 2 week (#5)	Postop 2 month (#6)	Postop 1 year (#7)
Consent	x								
Knee Radiograph		x	x		x	x		x	x
Identify Complications			x	x	x	x	x	x	x
Mayo Knee Sheet		x		x	x		x	x	x

SF-12 Version 1		x		x	x		x	x	x
Range Motion		x		x(artic.)	x		x	x	x
KSS Pre-Op		x							
KSS Post-Op				x	x		x	x	x
Assess Clinical Parameters				x	x		x	x	x
Satisfaction				x	x		x	x	x
Labs	x				x			x	x

Measurement Tools

At the time of reimplantation the surgeon would record whether the implant used would be a posterior stabilized design versus a varus valgus constrained condylar knee, versus hinged total knee.

Laboratory Parameters

Data points to be collected would include laboratory studies from the initial diagnosis, at the time of antibiotic stop date and immediately prior to reimplantation. This would include the Erythrocyte Sedimentation Rate and C-Reactive Protein at a minimum. We would also gather a complete blood count with differential prior to knee resection and, again, prior to reimplantation. We would analyze the microbiologic culture data from the time of resection and reimplantation. We would analyze the histopathology from the time of resection and the time of reimplantation.

Intraoperative Data

Surgical data collected would include surgical time as measured from the time of the skin incision to the time of final wound closure. The type of exposures needed (standard versus extensile, such as quadriceps snip, tibial tubercle osteotomy or other),

the level of prosthetic constraint required, intraoperative range of motion following capsular closure, complications between stages such as fracture, progressive bone loss, tendon or ligament injury, antibiotic complications, intraoperative blood loss, transfusion data. Classification of bone loss at 1st and 2nd stages. Classification will be done at the two surgical stages by the Anderson Orthopedic Institute classification [5] Which is a validated and reliable system of measuring bone loss which facilitates planning of total knee arthroplasty revision and rehabilitation and meaningful comparisons between different series of patients and treatment protocols.

Surgical Difficulty

Surgical difficulty will be assessed by a survey of the treating surgeons to rate from 1 to 10 the ease of surgery at the time of reimplantation.

Radiographic Parameters

Knee radiographs including an anterior-posterior view and true lateral view, and merchant view will be recorded preoperative, postoperatively after the resection, prior to the reimplantation, postoperatively after the reimplantation, at two months after reimplantation, and at the 1 year follow-up appointment. The radiographs will be evaluated for component fixation, component position, and alignment.

Mayo Knee Sheet

This is a clinical standard for rating efficiency of total knee replacement. It is a disease-specific test that has been validated and is used widely (presently the standard for current practice at the Mayo Clinic). This data will be collected at the time of diagnosis, prior to the knee reimplantation, at the time of Total Joint Registry follow up, 2 weeks, 8 weeks, and one year.

Knee Society Score

This is a clinical standard for rating the outcome of total knee replacement.[6, 7] It is a disease-specific test that has been validated and is used widely. The data can be obtained directly from the Mayo Knee Sheet. This data will be collected at the time of diagnosis, prior to the knee reimplantation, at the time of Total Joint Registry follow up, 2 weeks, 8 weeks, and one year.

SF-12 Version 1

This self-administered questionnaire has been validated for measuring and monitoring health status in large group studies. It has been published as the best measure for assessing general health for arthroplasty patients as noted in the analysis of the Swedish Registry.

Complications/Lost to Follow-up Form

Any serious complications that occur from the surgery will be documented. Sepsis, embolism, failure of primary wound healing, hemorrhage, prosthesis loosening, , skin necrosis, hematoma, approach extension, or periprosthetic fracture are possible complications. If for any reason a patient is lost to follow-up (will not return for office visits) there must be a form completed to indicate this event.

Satisfaction

This data will be available from the Mayo Knee Scoring sheet.

Medical Device

The revision total knee system, which will be used for both groups, has been FDA approved.

PARTICIPANT POPULATION

Inclusion Criteria

1. Male or female age 18 to 100.
2. Preoperative diagnosis of bacterial infection by culture which would include a preoperative aspiration and at least three intraoperative cultures. The preoperative aspiration would also be sent for a cell count with differential. All patients would have an ESR and CRP drawn in the preoperative phase. Patients with a negative preoperative aspiration, but an actively draining wound or draining sinus tract, would be considered as infected. Intraoperative histopathology would also be obtained in all cases of infected total knee replacement at the time of the resection.
3. Intact extensor mechanism.
4. Adequate soft tissue envelope (no requirement for soft tissue coverage such as a muscle flap or skin graft)
5. Adequate bone stock for knee reconstruction
6. Medical fitness for staged knee reconstruction

Exclusion Criteria

1. Known Atypical infection (mycobacterial or fungal)

2. Extensor mechanism disruption
3. Inadequate soft tissue envelope requiring muscle flap or skin grafting
4. Inadequate bone stock (T3 or F3 by the AORI classification)
5. Medical status precluding staged knee reconstruction
6. Requirement for hinged knee reconstruction at the time of reimplantation
7. Pregnant women – for women of child bearing age, a negative pregnancy test will be needed prior to enrollment to the study.

Recruitment

This will be carried out by the investigator. The study will be described to the patient, and a form of consent that states clearly the background and reasoning will be given to the patient.

We would plan to keep a running log of patients diagnosed with a chronic total knee infection who:

1) Refuse to enter the study.

2) Were not deemed to be appropriate candidates for the study and for which reason.

3) Have an Intraoperative conversion aside from the randomization to a different type of spacer or planned reconstruction design.

Competency

Study participants must be able to give informed consent.

Gender and Racial/Ethnic Distribution

No gender or racial/ethnic group will be intentionally excluded from this study.

Risks

Participation in this study poses no increased risk to patients undergoing 2 stage treatment of infected total knee arthroplasty. With any knee replacement, there is a possibility that the prosthesis will need to be removed and replaced and that the procedure may involve unforeseeable risks. Some of the known risks include failure to achieve firm attachment of the implant to the bone, fracture of bone during implantation, infection, deep vein thrombosis, neurovascular injury, wound problems, and anesthetic problems. In a some of cases, the knee prosthesis will loosen over years of use and pain and decreased mobility will occur.

Randomization of the Study Patients

In order to assign patients to specific treatment groups in an unbiased manner, randomization will occur prior to surgery. The assigned treatment codes for patients in each group will be generated by a computerized randomization program developed by the Division of Biostatistics. After the patient has met the entrance criteria, and given their full informed consent to participate in the study, they will be assigned to the treatment group. Patient randomization will be performed at the time of consent.

The randomization will be stratified on four variables with potential confounding effects on the outcomes of interest. Specifically, separate strata will be created by

surgeon (TMM, MJT, MPA, ADH, and KIP), gender (male vs female), age (<60 years vs ≥60 years), and BMI (<30 vs ≥30).

Statistical Methods and Sample Size

Several factors determine the appropriate sample size for a scientific clinical investigation. The following criteria are believed to be relevant for this study:

1. Selection of the level of difference between treatment results, if it exists, that the study desires to detect
2. A sample of sufficient size to provide statistical validity at a power level of 80 percent and an alpha level of 0.05.
3. A study and database size that is manageable to insure good data quality.
4. Consideration of expected subject attrition.

The two patient cohorts will be followed prospectively and evaluated with specific functional, clinical and radiographic outcome measures at 2 weeks, 2months and at a year from surgery. The principal outcomes include the treatment of infection, and the clinical result of the reimplantation, specifically pain and range of motion.

Power Analysis

For this study, we hypothesized that the articulating and static spacers would be equally efficacious at eradicating infection[4, 8]. A study by Haleem et al(CORR 2004) [2] The preoperative pain scores improved(p</=0.001) from a median of 49 points to a median of 89 points postoperatively. Preoperative functional scores improved

(p,/=0.001) from a median of 5 points to a median of 50 points (range, 0–100 points) postoperatively. The preoperative range of motion (ROM) in the 81 knees that did not have major surgery had a median of 85° (range 30°–125°), and the ROM at last follow-up had a median of 90° (range 30°–120°). The median change was an improvement ($p < 0.01$) of 10°, ranging from a loss of 55° to a gain of 80°. Using this data to generate estimates of variability, we calculated the sample sizes required to detect differences in ROM and also Knee Society scores, with 80% power. If we enroll 28 per group, and after 10% attrition end up with 25 per group, we will have 80% power to detect differences of at least 15 degrees in ROM, 10.5 points in knee pain score, and 17 points in knee function score. Any observed differences smaller than these will likely not be detected as significantly different. Therefore, the goal of the study would be to randomize a total of 56 patients with 28 patients in each arm of the study.

The participating surgeons would be TMM, MJT, MPA, ADH, and KIP. All of the surgeries would be performed at the Mayo Clinic in Rochester, Minnesota at either the Rochester Methodist or St. Marys Hospital campuses.

We expect to be able to enroll between 1-2 patients per month for this study from 5 surgeons (MJT, TMM, ADH, MPA, KIP). We expect to see at least 3 to 6 patients per month who would be candidates for the study. The total enrollment period is anticipated to be approximately 1 year, with an additional 15 months needed for performance of the procedure and follow-up.

The sample size feasible for this study is not adequate to be able to detect a statistically significant difference between the literature-estimated joint survival times of

revision total knee arthroplasty. The focus on joint survival in this study will instead be estimation with confidence intervals.

Patient demographics and outcomes will be described using mean ± standard deviation if continuous and distributed approximately Gaussian, or median (25^{th} percentile, 75^{th} percentile) if continuous but not Gaussian. Categorical variables will be described as count (percent). Outcomes of primary interest will include the range of motion, quality of life as measured by the SF-12, and Knee Society scores, at 2 weeks after resection, prior to reimplantation, 2 weeks after reimplantation, 2 months, and 12 months. The two treatment groups will be compared on these outcomes using two-sample t-tests if the data are approximately Gaussian. If the data are not sufficiently normal, Wilcoxon rank sum tests will be used. In-hospital and perioperative complications such as periprosthetic fracture (intraoperative and postoperative), deep vein thrombosis, pulmonary embolus, neurovascular complications, infection and mortality will be compared using chi-square tests or Fisher's exact tests if necessary and appropriate. Analysis of time to event outcomes such as fracture, complications related to the surgical procedure, the need for revision surgery and survival will utilize survival techniques such as the method of Kaplan and Meier and Cox proportional hazards models. All statistical tests will be two-sided and p-values less than 0.05 will be considered statistically significant. SAS v9.1 (SAS Institute INC, Cary, NC) will be utilized.

POTENTIAL CONFLICT OF INTEREST FOR INVESTIGATOR

The principal investigators (MJT, TMM, MPA, ADH, and KIP) of this study do not have a direct financial interest in the study implants or the surgical techniques.

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