Open vs Arthroscopic Treatment of Septic Arthritis in the Adult Native Knee: A Prospective Trial

"Study Protocol and Statistical Analysis Plan"

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University Medical Center of El Paso

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PROTOCOL

Study Title: Open vs Arthroscopic Treatment of Septic Arthritis in the Adult Native Knee: A Prospective Trial

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Abstract:

Septic arthritis is defined as a pathologic inoculation of a joint by direct or hematogenous means rather than an immunologic response to pathogens as that seen inflammatory arthropathies.[1] The gold standard for diagnosis of septic arthritis is a positive gram stain or subsequent positive cultures from arthrocentesis.[2] Cultures may require multiple days in order to result in growth of the causative organism and delay in treatment can result in degenerative joint changes, osteonecrosis, or joint instability.[3, 4] The pathogenesis begins as the bacteria induces synovial cells to secrete proteolytic enzymes[5] that can result in cartilage damage as early as 8 hours after infection[6] with subsequent proteoglycan and collagen destruction.[7] As the infection progresses, the intra-articular pressure rises with further compression and thrombosis of the synovial vasculature thus enhancing cartilage damage.[8] Therefore, prompt establishment of diagnosis and providing early intervention is paramount for treatment outcomes.

The typical signs and symptoms of adult septic arthritis include an edematous joint with surrounding erythema that is warm and tender to palpation. Some common risk factors include, but are not limited to: rheumatoid arthritis, diabetes, renal disease, or recent bacteremia.[1, 2, 9-11] The classic modality to diagnose septic arthritis in patients with suspected septic arthritis is to perform an arthrocentesis. A synovial white blood cell count of 50,000 cells/mm^2 is highly suggestive of septic arthritis[12], although lower numbers have been cited as well.[13] Other laboratory values can be utilized in conjunction such as serum procalcitonin[14], IL-6[15], or lactate.[16] Ultimately a summation of the patient's overall clinical presentation, risk factors, and laboratory values is the best way to establish a diagnosis of septic arthritis.[17]

Surgical excisional debridement is the main stay of management with necessary decompression, lavage, debridement, and partial synovectomy.[17] However, there has been considerable debate over the optimal modality. Most surgeons perform an open arthrotomy or arthroscopic debridement, although serial aspiration can be considered as an option in very limited circumstances with patients who cannot tolerate surgery.[18, 19] While open arthrotomy has been often utilized, there has been an increasing number of proponents for arthroscopic treatment citing lower re-infection rates and better functional outcomes.[20-23] However, there has been a lack of well-designed prospective studies comparing surgical treatment modalities for native knee septic arthritis. The goals of this present study are to determine if arthroscopic management of septic arthritis in the native knee resulted in lower number of surgeries and shorter length of stay compared to open arthrotomy. Secondary outcomes included differences in functional outcome and overall patient satisfaction.

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Hypothesis: There is a significant difference in hospital length of stay and the number of surgeries required to provide clinical resolution of septic arthritis in an adult native knee when treated with arthroscopic versus open irrigation and debridement.

Background (literature review): Please see abstract

Specific Aims: To determine if there is an overall difference in hospital length of stay and number of surgeries required to provide clinical resolution of septic arthritis of an adult native knee. Secondary outcomes will evaluate differences in knee range of motion, post operative pain levels, and overall patient satisfaction.

Significance of this study (why is it important, what new information will it provide?)

Currently the recommended treatment for septic arthritis is surgical irrigation and debridement in an urgent manner (<24 hours from presentation). However, with the increasing utilization of arthroscopic approaches to orthopedic cases, there has not been an established optimal surgical approach to intra articular knee irrigation and debridement. Surgeons most often rely on their own preference (i.e. arthroscopic versus open approaches), however there has not been an established optimal surgical approach. Ultimately all patients undergo operative management (and repeated trips to the operating room, if needed). However, newer retrospective studies have shown clinical benefit with

shorter hospital stays, lower number of repeated trips to the operating room, and overall improved patient satisfaction when treated with arthroscopic surgical management of septic arthritis of the knee.

This study would help solidify in a randomized control trial the most appropriate surgical approach to septic arthritis of the adult native knee.

Study Design & Methods (include the following information):

Human Study Subjects:

A.) Informed consent process and timing of obtaining consent

Study recruitment will take place in the emergency department. All adult patients (>18 years) who have a clinically established diagnosis of septic arthritis in the emergency department based on the following will be considered for study inclusion and approached for offering participation in our study:

- Arthrocentesis with synovial WBC > 50,000 with left shift (85% PMNs)
- Acrystalline (without gout crystals) elevated synovial WBC >25,000 with high clinical suspicion
- Willingness to participate in this research study

Once the arthrocentesis results have confirmed the above inclusion criteria, the orthopedic resident who is managing the patient's care will contact one of the study investigators. In the meantime, the orthopedic resident managing the patient's care will obtain consent for surgery and book the patient for the operating room to ensure there is not a delay in patient care.

One of the study investigators will perform a face to face introduction of the study to the patient in the emergency department prior to the operative management. Their diagnosis of septic arthritis of the knee will be explained in thorough detail with the assistance of a Language Line Solutions certified translator if the patient is Spanish speaking. Informed consent for study inclusion will be obtained if the patient meets the above inclusion criteria.

It must be emphasized that the patient's care is not to be delayed in order to obtain consent for study inclusion. The study investigators include multiple orthopedic attending surgeons and residents. However, a situation may arise in which the study investigators are NOT available to explain the study and obtained informed consent. In this case, the patient's care is not to be delayed in order to ensure their inclusion in this study. They will be treated promptly to ensure appropriate patient care and will not be included in this study.

B.) If non-English speaking persons will be enrolled, state the informed consent process for enrolling the subjects, including who will conduct the consent interview, translated documents, etc. Exclusion of non-English speaking subjects from research requires ethical and scientific justification

All non-english speaking persons will be offered study inclusion. Informed consent will be obtained utilizing a Spanish-translated consent form (after IRB approval). There are multiple Spanish speaking members of the research personnel and they will be obtaining Spanish consents. If one is not available, then a certified hospital interpreter will be utilized. If none are available, since UMC does not allow language line solutions to be used for research purposes, the patient will not be able to be consented and thus will not be included in the study.

C.) Indicate the population of subjects potentially able to participate in this study

All adult patients (>18 years) who have a clinically established diagnosis of septic arthritis in the emergency department based on the following will be considered for study inclusion and approached for offering participation in our study:

-Arthrocentesis with synovial WBC > 50,000 with left shift (85% PMNs)
-Acrystalline (without gout crystals) elevated synovial WBC >25,000 with high clinical suspicion
-Willingness to participate in this research study

These patients are all indicated with formal operative irrigation and debridement of their knee, regardless of study inclusion. However, they will be excluded from study inclusion if they meet one of the following exclusion criteria:

- Recently treated septic arthritis (within past 3 months)
- If they have a prosthetic joint replacement to the affected knee
- Refusal to participate in the study

D.) Indicate the number needed

Our power analysis (beta =0.80, alpha = 0.05) shows the optimal sample size to be a minimum of 40 patients.

E.) List the inclusion/exclusion criteria

All adult patients (>18 years) who have a clinically established diagnosis of septic arthritis in the emergency department based on the following will be considered for study inclusion and approached for offering participation in our study:

-Arthrocentesis with synovial WBC > 50,000 with left shift (85% PMNs)
-Acrystalline (without gout crystals) elevated synovial WBC >25,000 with

high clinical suspicion
-Willingness to participate in this research study

These patients are all indicated with formal operative irrigation and debridement of their knee, regardless of study inclusion. However, they will be excluded from study inclusion if they meet one of the following exclusion criteria:

- Recently treated septic arthritis (within past 3 months)
- If they have a prosthetic joint replacement to the affected knee
- Refusal to participate in the study

F.) Vulnerable populations

Patients with altered mental status at the time of presentation. In accordance with current guidelines, a legally authorized representative may provide consent for inclusion in this study. If a legally authorized representative is unavailable, the patient will not be considered for inclusion in this study.

G.) Describe the method of identifying and recruiting subjects and any screening

All adult patients (>18 years) who have a clinically established diagnosis of septic arthritis in the emergency department based on the following will be considered for study inclusion and approached for offering participation in our study:

-Arthrocentesis with synovial WBC > 50,000 with left shift (85% PMNs)
-Acrystalline (without gout crystals) elevated synovial WBC >25,000 with high clinical suspicion
-Willingness to participate in this research study

These patients are all indicated with formal operative irrigation and debridement of their knee, regardless of study inclusion. However, they will be excluded from study inclusion if they meet one of the following exclusion criteria:

- Recently treated septic arthritis (within past 3 months)
- If they have a prosthetic joint replacement to the affected knee
- Refusal to participate in the study

H.) Define how long each subject will be studied

Approximately 6 weeks after discharge (the hospital length of stay will be variable depending on patient comorbidities).

I.) Describe any compensation given to subjects

This study will NOT be offering compensation to any subjects.
Describe the following aspects of the study design:

A.) Proposed study groups with number/group and treatments/group

Group 1: patients who undergo open surgical incision and drainage with debridement and irrigation (>20 patients)

Group 2: patients who undergo arthroscopic incision and drainage with debridement and irrigation (>20 patients)

B.) Describe the method used to determine the number of subjects needed

Power analysis utilized to determine a difference in the number of surgeries required to display apparent clinical resolution between open versus arthroscopic treatments (beta =0.80, alpha = 0.05) shows the optimal sample size to be a minimum of 40 patients.

C.) Describe how you determined that this number of subjects could be recruited

Power analysis. Additionally, Dani Joyner (CHRC/Research Manager MC EP Compliance) was contacted and was able to find a preliminary potential of 1,851 unique patient records from the year 2000 to the present who had septic arthritis. Even if only 20% of these patients met study inclusion/exclusion criteria, approximately 20 patients a year would be included. This would require 2-3 years of data collection in order to meet appropriate power analysis.

Anecdotally, the attending physicians serving as principal- and co-investigators believe they treat a minimum of 20 adult patients each per year with septic arthritis of the native knee.

D.) Method of randomization

Patients with medical record numbers ending in an EVEN number will undergo open surgical irrigation and debridement.

Patients with medical record numbers ending in an ODD number will undergo arthroscopic surgical irrigation and debridement.

E.) Schedule of events (i.e. control vs. treatment, number of visits)

All patients who present to the emergency department with a painful knee and clinical suspicion for septic arthritis undergo appropriate workup by the emergency department staff members. If there is a clinical suspicion for septic arthritis, the standard workup includes the following:

-assessment of vitals
-obtaining a history of the present illness
-performing an appropriate physical examination

If a provider determines that septic arthritis is part of their differential diagnosis, a basic serum laboratory workup is to be ordered. There will be a template created on the Cerner application to assist providers with a convenient, expedited manner of ordering these labs. These will include the following blood serum values:

-complete blood count with differential (CBC w/ diff)
-complete metabolic panel (CMP)
-erythrocyte sedimentation rate (ESR)
-c-reactive protein (CRP)
-total protein
-blood cultures

Septic arthritis is destruction to the chondrocytes and places patients at risk for accelerated degenerative arthritis, abscess formation, and osteonecrosis. Therefore, establishing a timely diagnosis and initiating definitive management (i.e. surgical debridement) is of utmost importance. If the clinical suspicion is high enough, providers may perform an arthrocentesis of the knee prior to waiting for the aforementioned labs to return with results from the lab. Otherwise they should await results and determine if infectious etiology should be included. When providers perform arthrocentesis, the following laboratory markers will be included in the synovial fluid analysis (also through a templated order set on Cerner):

-cell count with differential
-gram stain
-crystal analysis (for gout)
-aerobic cultures x3
-anaerobic cultures x3
-fungal cultures x3
-acid fast bacilli

The gold standard method to establish the diagnosis of septic arthritis is positive bacterial growth on cultures. However, this may take days and ultimately delays treatment. Thankfully there is a plethora of research for predictive blood serum and synovial fluid laboratory markers, which have been included above.

At any point during the initial emergency department presentation the emergency department may consult orthopaedic surgery, in which an orthopaedic surgery resident may continue the appropriate workup.

All adult patients (>18 years) who have a clinically established diagnosis of septic arthritis based on the following will be considered for study inclusion:

- Arthrocentesis with synovial WBC > 50,000 with left shift (85% PMNs)
- Acrystalline (without gout crystals) elevated synovial WBC >25,000 with high clinical suspicion
- Willingness to participate in this research study

These patients are all indicated with formal operative irrigation and debridement of their knee, regardless of study inclusion. However, they will be excluded from study inclusion if they meet one of the following exclusion criteria:

- Recently treated septic arthritis (within past 3 months)
- If they have a prosthetic joint replacement to the affected knee
- Refusal to participate in the study

If the diagnosis of septic arthritis has been established, the diagnosis, pathogenesis and treatment options will be discussed with the patient. The current standard of care for the management of septic arthritis in the knee is operative incision and drainage of the joint with debridement and irrigation, obtaining intra operative cultures, then initiating antibiotic therapy. Non operative management would consist of antibiotic treatment alone. Should the patient decide to proceed with surgical intervention, an informed consent for surgery in the presence of a witness will be obtained, as per standard guidelines. At that time, the patient will be asked to participate in this study. If they agree, then the patient will be randomized into one of two groups:

1. Open surgical incision and drainage with debridement and irrigation
2. Arthroscopic incision and drainage with debridement and irrigation

An informed consent will be performed by one of the participating research investigators in the setting of a witness, as per standard guidelines. The surgical consent will be obtained at that time in a similar manner. If the patient declines to participate in this study, they will still be offered surgical intervention based on physician preference and their surgical ability.

All patients will be admitted after surgery for continued intravenous antibiotics and infectious disease consultation. Additionally, they will be followed for signs/symptoms that indicated a second surgery is required. The specific criteria for recurrence and failure of initial irrigation and debridement will be the following:

-persistent purulent discharge from a drain or incisional site
-increasing pain
-decreasing range of motion
-persistent fevers
-persistent elevation of serologic inflammatory markers

Patients showing steady clinical improvement after 72 hours post operatively will be discharged with continued antibiotic therapy targeted to bacteria if positive growth on cultures. If delayed growth occurs after patient discharge, they will be individually contacted for change to antibiotics if deemed appropriate, as is standard clinical practice. All study participants will have regularly 2-week and 6-week post-operative appointments where functional outcomes will be assessed in include physical exam, knee Lysholm scores and basic laboratory evaluation.

Vitals, physical exam findings, and laboratory markers will be recorded in the clinical record and maintained within the patient's electronic medical record. The principal investigator will utilize the electronic medical record to record and maintain pertinent physical examination findings, laboratory markers, and treatments on a private, secured device. The only individuals who will be granted access to the device are co-investigators participating in this research study.

F.) List of Key Variables or Measurements to be done

-initial presenting arthrocentesis labs as well as serum lab values
-physical examination findings
-time from presentation to operative management
-type of surgical approach performed
-total operative time
-reason for necessity to return to operating room
-number of operative procedures required in order to establish clinical improvement
-bacterial growth from arthrocentesis and operative cultures
-length of antibiotic course as deemed by infectious disease specialist
-hospital length of stay
-Lysholm knee scores

G.) Assessment of subject safety and development of a data and safety monitoring plan

All data will be stored on a password locked external hard drive device. The password will only be provided to primary investigators of this study. The information recorded will be maintained on this device and stored in accordance with TTUHSC policies. The principal investigator will be responsible for version control and will ensure the study data are shared among team members in a secure fashion in accordance with TTUHSC/UMC guidelines (e.g., encrypted email, restricted-access share portal). The original email communications will be permanently deleted from the principle investigator's email inbox, outbox, and deleted folders.

Any unanticipated problems or other adverse events will be reported to the TTUHSC Human Protections Administrator. All unanticipated problems involving risk to subjects or others, adverse events, and all concerns related or possibly related to the study will be reported promptly to the TTUHSC Human Research Protections Office by providing

initial notification of the event as quickly as possible after the research team's knowledge of the event, but within five (5) business days.

H.) Create and attach your data collection form

This has been completed and filed with the IRB submission.

I.) Methods of data analysis (statistical analysis)

Both Dr. Childs and Dr. Fernandez have served as statisticians in their previous roles as research assistants and have advanced training in statistical analysis. Regardless, the finalized data will be submitted to Texas Tech statisticians for validation and confirmation. Some of the anticipated statistical analysis tests are as follows:

Independent samples t-tests will be used to compare means of continuous and ordinal variables and p values less than 0.05 will be considered to represent a significant difference. For variables with Levene's Test for Equality of Variances greater than 0.05, equal variance is assumed. Pearson Chi-Square test p-values less than 0.05 will be considered to represent a significant difference in categorical variables. Fischer's exact test less will not be utilized as NCDB groups with $n<10$ are not to be included. ANOVA will be used to calculate significant differences in continuous and ordinal variables that have more than two categories. Paired samples t test and repeated measures ANOVA will be used to determine the progression of individual patients over time for continuous and ordinal variables respectively. Wilk's Lambda p-value less than 0.05 will be considered significant for repeated measures ANOVA and pairwise comparison will be used to determine the location of significance. Binary logistic regressions will be used to calculate odds ratios. Multivariate binary logistic regression may be attempted for all

significant variables. Receiver Operator Characteristic (ROC) may be calculated for significant continuous variables to determine the existence of a threshold that maximized sensitivity and specificity. All analysis will likely be performed by Dr. Childs on SPSS version 25 (IBM Corp. Released 2018. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).

Sites where study will be done

University Medical Center of El Paso

4815 Alameda Ave

El Paso, TX 79905

Risks

We do not anticipate any unexpected risks, as patients will be receiving appropriate care regardless of surgical approach to which they are randomized.

Possible benefits to subjects

None. Again, they will all undergo appropriate operative management of septic arthritis of the knee in an urgent manner. However, they will be part of a study that (possibly) establishes the most appropriate surgical approach.

Confidentiality measures

This study requires collecting patient medical record numbers (MRNs) and patient ages over 89, both of which are considered private health information (PHI). Therefore, a separate master list containing PHI will be established in order to assign patients a "subject identification number (ID)." This subject ID variable will serve as an added measure of confidentiality. No patient PHI will be reported in the manuscript of this study nor any of the tables/figures included. The final manuscript will be provided to the appropriate Texas Tech University Health Sciences Center research committees for review prior to submission to a peer-reviewed journal.