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Prospective randomized study investigating the characterization of elution of antibiotics from antibiotic impregnated cement after total knee arthroplasty

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OVERVIEW

Background information:
Antibiotic cement is commonly used in primary total knee arthroplasty. It has mixed evidence for reducing infection rates after total knee arthroplasty. Some surgeons utilize pre-mixed antibiotic cement, while others hand mix the same dose of antibiotic into plain cement. The difference in antibiotic elution of pre-mixed versus hand-mixed antibiotic bone cement is unknown. The cost of hand-mixed cement is significantly less than that of pre-mixed cement. Therefore, investigating any difference between the two types of cement could potentially lead to enormous cost savings for the healthcare system. For cementless knees surgeons typically add an antibiotic to the knee prior to closing the incision to reduce infection.

Additionally, prior studies have shown the majority of organisms causing infection after primary total knee arthroplasty are resistant to aminoglycosides, the major antibiotic class present in pre-mixed antibiotic cement. Vancomycin is an ideal antibiotic to use in antibiotic cement as it is heat stable and effective against the Staphylococcal species that commonly cause prosthetic joint infection after total knee arthroplasty. In-vitro analyses have shown vancomycin elution to be unpredictable from antibiotic bone cement. However, the addition of an aminoglycoside in similar studies have shown it to improve vancomycin elution in a synergistic manner. Therefore, we also seek to investigate the synergistic effect, if any, of vancomycin and tobramycin together on vancomycin elution rates after primary total knee arthroplasty with antibiotic laden cement.

Primary Hypothesis:
The antibiotic elution profile will be the same for hand-mixed and pre-mixed antibiotic in polymethylmethacrylate bone cement. Tobramycin and vancomycin together will synergistically improve elution profiles of each other. The elution levels of vancomycin drained from the knee will be very minimal and is an effective way to reduce joint infections.

Aim(s):

1. Determine any difference in elution of antibiotic from pre-mixed and hand-mixed antibiotic cements with tobramycin
2. Determine the synergistic effect, if any, of vancomycin and tobramycin together in antibiotic cement
3. Determine the elution level of antibiotic from the knee in a cementless total knee arthroplasty

Potential Contribution:
The findings of this study will provide evidence for optimal antibiotic choice in antibiotic cement used in total knee arthroplasty, as well as determine the effect of using surgeon-mixed versus pre-mixed antibiotic cement on elution of antibiotics from the cement. The findings will also determine the effect of using antibiotic powder in the wound prior to closure in a cementless total knee arthroplasty.

METHODS
Timeline: 1 year 6 months (1 year of prospective enrollment and 6 months of data analysis.)

Data analysis will begin after this study has received approval. Anticipated end date is January 2020.

Inclusion/Exclusion Criteria:

1. Age over 18
2. Total knee arthroplasty for primary osteoarthritis performed by Dr. Rick Wright and Dr. Charles Lawrie and Dr. Robert Barrack. Primary diagnosis of knee osteoarthritis

Exclusion criteria:
1. Diminished mental capacity
2. Vancomycin allergy
3. Tobramycin allergy
4. Chronic kidney disease stage III and stage IV

Recruitment:
We will be identifying patients from the clinical practice of Dr. Rick Wright and Dr. Charles

Lawrie and Dr. Robert Barrack.

Design:
This study is a prospective, randomized, study designed to characterize and quantify the level of antibiotics eluted from antibiotic laden cement after primary cemented total knee arthroplasty and the level of antibiotics eluted from the knee after cementless total knee arthroplasty

The study will collect intraoperative fluid postoperative intraarticular drain fluid from the total knee arthroplasty the day after surgery. The fluid being used for the study is fluid that is drained after surgery and discarded. Data collected will permit clinical evaluation of antibiotic cement types as they pertain to total knee arthroplasty knee pre-operative and postoperative. This study will collect implant-related or possibly implant-related adverse events. Data collected will include the following: Patient demographics (age, gender, BMI), implant and surgical information, medical comorbidities and intraarticular findings. Each eligible participant will be required to execute written informed consent and covers the provisions of this study.

Number of participants: We propose to enroll 58 participants. A randomization schedule will be determined at the initiation of the study for assigning the first 24 patients to one of four antibiotic cement study groups, we will then review and proceed with a randomization schedule for the next 24 patients to one of four antibiotic cement study groups:

Pre-mixed tobramycin

Hand-mixed tobramycin

Hand-mixed vancomycin

Hand-mixed vancomycin and hand-mixed tobramycin

Enrollment will provide 1:1:1:1 study group ratios

The study patients will be blinded to their study group. The surgeons and study personnel will not be blinded to study group.

10 patients will be in the cementless group.

Data collection:
Data collection for prospective patients will occur preoperatively and postoperatively.

Data analysis:

A student t-test will be used to compare means and standard deviations between study groups for the variable which this test methodology is appropriate. Descriptive statistics will be used to analyze the subjective data points such as AEs. Analysis methods will be further discussed during data and publication review meetings. We will be doing analysis at pre-operative, intraoperative and postoperative. An independent statistician, independent of the study team and the orthopedics department will analyze the data.

Procedures:
The study will collect intraarticular drain fluid from the total knee arthroplasty the day after surgery. There will also be a chart review.

INFORMED CONSENT
Enrollment and consent will begin in the clinics of Dr. Rick Wright and Dr. Charles Lawrie The treating surgeon will identify patients who are determined to be candidates for primary TKA, and who generally meet the study requirements.

The consent process will occur by one of the following means:

1) The study coordinator will meet with each potentially eligible participant to review the study requirements (including additional screening for eligibility) and answer any questions the patient may have.

If the patient has any clinical questions that cannot be answered by the study coordinator they will be answered by the physician or the physician's nurse. The patient will have the opportunity to review the consent form, discuss with family/friends, and do his/her own research on the subject if desired. Qualified patients who agree to participate in the study will be required to sign an Informed Consent Document. Valid enrollment is not granted until after surgery, once it has been verified that the participant has had total knee surgery.

2) The consent discussion and review of the Informed Consent Document may occur over the phone. In this case, the study coordinator will call the patient to present the study to the participant and gauge interest in participation. If the patient expresses interest in participation, the study coordinator will e-mail, mail or fax the Informed Consent Document to the participant. The patient will be given the opportunity to ask questions. If the patient has any research questions beyond the scope of the study coordinator, arrangements will be made for the participant to speak with the applicable member of the research team, including the PI. After review of the Informed Consent Document, the participant will sign the applicable sections of the Informed Consent Document and mail or fax the consent for back to the study coordinator. The Informed Consent Document will be signed by the consenting study coordinator upon receipt. Valid enrollment is not granted until after surgery, once it has been verified that the participant applicable member of the research team, including the PI. After review of the Informed Consent Document, the participant will sign the applicable sections of the Informed Consent Document and email, mail or fax the consent for back to the study coordinator.

PROCEDURES FOR MAINTAINING CONFIDENTIALITY

Data Security:

Protection of confidentiality by the Washington University Coordinating Center will be maximized by use of (a) protected and secured data collection, (b) password protected access to data storage, and (c) access to patient data limited to the study coordinator or his designate.

ASSESSMENT OF RISKS AND BENEFITS

Risks

A potential risk of accidentally disclosing information regarding Washington University patients is possible though unlikely.

Benefits

The findings of the study will identify areas for improvement in antibiotic choice used for total knee arthroplasty and comparing different types of antibiotic cement used in total knee arthroplasty.

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