Topical Vancomycin in Neurosurgical Wound Prophylaxis

NCT02284126

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Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAN3703(M03Y07)	**Protocol Status:**	Approved
Enrollment start date:	10/21/2014	**Expiration Date:**	02/04/2021

Principal Investigator: Connolly MD, E. Sander

Title: Topical Vancomycin for Neurosurgery Wound Prophylaxis

Lead Institution/Coordinating Center

Columbia University Medical Center is the lead institution. Patient enrollment will occur at Columbia University Medical Center and Weill Cornell Medical Center. Mount Sinai department of Biostatistics is responsible for data monitoring and security. The distribution of personnel is as follows:

Columbia University Medical Center

Principle Investigator

- Clinical/Study Coordinator

Weill Cornell Medical Center

Lead Investigator

- Clinical/Study Coordinator

Mount Sinai

Biostatistician

Description of the responsibilities of the coordinating center / lead institution with regard to communication and training of research personnel across sites:

The lead institution will organize two meetings per month to involve the study coordinator for each patient enrollment site. Each site is to host the meeting once per month. Each site has a history of IRB approval and trained personnel; thus, each site is responsible for training new personnel. The coordinating center will ensure Weill Cornell's training is in accordance with their institutional IRB. The coordinating center will schedule quarterly data and safety monitoring board (DSMB) meetings to include site principle investigators, site coordinators, and members of the DSMB.

Plan to ensure that collaborating sites do not begin any research-related activity until IRB approval has been granted for the conduct of research at that site:

Each site has active IRB approval for research activities related to the study of topical vancomycin for

neurosurgery wound prophylaxis and trained personnel.

Description of the transmission of data to the data coordinating center:

REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Site coordinators enter data through the web-based portal which is securely monitored and hosted at Mount Sinai.

Data is analyzed when interim analysis is indicated by the data and safety monitoring board or when the biostatistician dictates it is necessary. Official interim analysis is conducted by the biostatistician at Mount Sinai.

Data for quarterly safety reporting is prepared by site coordinators and analyzed by the data and safety monitoring board.

Background

Study Purpose and Rationale:

Surgical-site infections (SSIs) occur in up to 500,000 patients per year in the United States.
Patients with SSIs require significantly longer hospital stays and higher healthcare expenditures. In fact, it is estimated that SSIs are responsible for almost 4 million excess hospital days and billions of dollars in added hospital charges every year. Additionally, SSIs are a significant source of morbidity and mortality for surgical patients. Thus, prompt and definitive measures are necessary in order to redress this significant public health concern. Over the past few decades, the implementation of a number of preventative measures—including improved techniques in pre- operative skin antisepsis and antibiotic prophylaxis—have led to significant reductions in the rate of SSIs. Studies have demonstrated that approximately half of all SSIs are preventable with the proper use of prophylactic antibiotics. Despite these dramatic improvements, SSIs remain a tremendous burden on the healthcare system. Our unpublished analysis of the National Inpatient Sample (NIS) in 2010 identified 117,000 craniotomies with a 2.4% rate of infection and 1.37% rate of MRSA-associated infection. Extrapolating to the full national population, there were 585,000 craniotomies and 14,040 post-operative infections. Published series report the rate of infection in intracranial neurosurgery to range from 1% to as high as 11%. This rate varies depending on the presence of hardware, prior radiotherapy, procedure duration, re-operation, and the presence of a CSF leak. The 30-day outcome associated with SSI following craniotomy was recently reported to be minor disability in 12.8%, major disability in 7.7% and death in 5.1%. The financial burden of nosocomial infection in neurosurgery makes up a disproportionate component of the total national cost burden. A study of nosocomial infection in the US in 1995 estimated a per-patient cost of $2100 and a total cost of $4.5 billion while a recent British study focusing on post craniotomy SSI identified a per-SSI cost of £9283, or $14,166. Given the tremendous potential for lifelong morbidity and mortality as a result of cranial SSIs, further reductions in the rate of SSI would be essential for the benefit of neurosurgical patients, as well as for the healthcare system as a whole. Topical formulations of vancomycin offer the possibility of direct application to the surgical wound, with minimal additional systemic drug exposure. Adjunctive vancomycin powder applied topically to surgical wound edges has been shown to significantly lower the SSI rate in both cardiothoracic surgery and spinal surgery. Importantly, laboratory analyses of blood and wound drainage samples from patients treated with vancomycin powder have demonstrated high vancomycin concentrations in the surgical wound, and simultaneously low drug concentrations in the peripheral blood, thereby confirming minimal systemic absorption in the setting of enhanced protection of the surgical site. Furthermore, there have been no reports of an increased rate of drug-related complications with the addition of vancomycin powder to standard antibiotic prophylaxis regimens.

Study Design:

This study has been designed as a single-blinded, multi-center, randomized clinical trial at New York Presbyterian Hospital Columbia and New York Presbyterian Hospital Cornell. The study population includes all adult neurosurgical procedures for which there exists clinical equipoise performed at each institution over a 4 year and 9 month time period. The treatment variable is the application of topical vancomycin to the surgical site. If a craniotomy is performed, a paste made from vancomycin powder and sterile solution will be applied to the edges and outer surface of the craniotomy. In all subjects of the treatment group, the powder will be applied directly to the wound prior to the closure of skin or galea. The primary endpoint is the rate of SSI 30 days after the operation. Secondary endpoints include vancomycin levels in serum, CSF, and drain output as well as changes in patient flora collected from the skin and nares preoperatively, 1-2 days postoperatively, 10-14 days post-operatively, and 90 days post-operatively. Research will commence after both Columbia and Cornell have obtained IRB approval, and after each institution has notified the other of this approval. This study is not intended to be reported to the FDA as a well-controlled study in support of a new indication, nor is there intent to use it to support any other significant change in the labeling or advertising of the drug.

Statistical Procedures:

The average baseline rate of SSI in neurosurgical craniotomies at the two participating hospitals was 1.8% in 2012 with the standard of care site preparation, draping, and perioperative intravenous antibiotics. Based on a systematic review of the intraoperative application of vancomycin powder in the surgical site during spinal surgery, we hypothesize that we would reduce the baseline rate by 75% to a new rate of 0.45%. Our power calculation indicate that we will need 1278 patients per group (2556 total) to achieve 90% power with a two-sided test at the 0.05 level. To account for the interim analysis, we increase the sample size by 3%. We therefore plan to enroll 1316 patients in each study group for a total of 2632 patients. The expected yearly total of patients undergoing craniotomies at the two participating centers is approximately 1150 patients per year. We expect approximately 5% of these patients to be ineligible due to impaired renal function, infection at or adjacent to the operative site, allergy to vancomycin, or lack of surgical closure of the dura or dural substitute, and an additional 25-40% of eligible patients to decline to participate in the study. An intention-to-treat analysis will be performed, requiring that patients are randomized, undergo surgery, and have a closed wound. Patients randomized to the variable group will be included in the per protocol analysis if they are randomized to the topical vancomycin group, actually have application of the vancomycin paste to the bone flap and skin edges as prescribed, and complete 30-day follow-up. Patients randomized to the non-variable group will be included in the per-protocol analysis if they complete surgery, do not receive topical vancomycin, and complete the 30-day follow-up. We anticipate that we will have infection status at 30 days for all patients irrespective of whether or not they continue the study. The primary subgroup of interest is patients undergoing craniotomy for which the power analysis has been performed. Other a priori subgroups of interest include: (1) surgeries involving implantation of foreign bodies including implantation of stimulation electrodes, implantation of recording electrodes and grids, and implantation of ventricular shunts; and (2) non-instrumented spine surgery. (3) patients with cephalosporin or penicillin-family antibiotic allergies that will already be receiving intravenous vancomycin as standard practice, to assess any added benefit of additional topical administration. Any missing values will be imputed using multivariate imputation of chained equations. We will report maximum likelihood estimates of ORs and other measures of association for point estimation along with two-sided 95% confidence intervals. Summaries of all participants randomized and the number who complete visits at after the day of randomization will be provided

for each treatment group. The treatment groups will be compared at baseline with respect to demographics, baseline measurements related to efficacy and baseline measurements related to safety. All outcome measures will be described in a univariate analysis. For continuous variables means and standard deviations will be calculated. For discrete and dichotomous variables, we will use contingency tables. For Aim 1 we will use a logistic model to determine the effect of topical vancomycin on surgical site infections at 30 days. For Aim 2 a multivariate analysis of the vancomycin levels in the serum, cerebrospinal fluid, and the wound drainage over the first 48 hours will be performed using mixed effects models. Patients who received intravenous vancomycin will be analyzed separately. For the discrete outcomes of Aim 3, we will use generalized estimating equations (GEE) to fit logistic models and log-linear models, with presence of vancomycin resistance and number of vancomycin resistant organisms as the respective response variables that account for the dependency of the repeated measures. Thirty-day survival will be estimated using Kaplan-Meier curves. Survival time will be defined as the time (in days) between randomization and death before 30 days. All patients who are still alive at day 30 after randomization will be censored. To compare the vancomycin arm with the control arm we will use the log-rank statistic. Nine interim analyses and one final analysis are planned for this trial. These analyses will be performed when increments of 0.1 fraction of the total number of participants will have finished the 30 day-assessment of the primary outcome. We will use an alpha-spending function with O'Brien-Fleming boundaries as a guideline for decision-making. At each interim analysis the value of the test statistic z-score will be compared with two critical values for the z- score: an upper critical value and a lower critical value. The alpha values associated with each interim analysis will be determined according to the formula (t*) = 2-2(z/sqrt(t*)). If the test statistic z-score exceeds the upper critical value, this will be considered significant.

Funding

Award Type	Funding Source Name	Name of awarding agency	Status	Award # or Application Date	Federal/State /Local Government Direct or Subcontract	What is the award covering?	Rascal PT Number
Federal/State / Local Government	HHS - AHRQ	Agency for Healthcare Research and Quality/DHHS	Awarded/Rec eived	1R01HS0229 03	Direct Recipient: With Subcontract Sites	Entire Protocol	PT-AABI1260
	Subcontract site(s), procedures taking place at each site and FWA# for federally funded studies: Cornell University Medical Center, full trial participant utilizing the study drug vancomycin. Mount Sinai, study biostatistician for the study.						

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Subcontract	Mount Sinai	Domestic	New York, NY	No, approval is not required	No, approval is not required
Subcontract	Cornell University	Domestic	New York, NY	No, but will be obtained (approval pending)	No, but will be obtained (approval pending)
Columbia/CUMC	Physicians & Surgeons building cerebrovascular lab				

Privacy & Data Security

This study involves the receipt or collection of Sensitive Data including Personally Identifiable Information (PII), Protected Health Information (PHI), and a Limited Data Set (LDS). If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

All physical documents will be stored in locked cabinets in a locked office only accessible by approved study staff. Electronic data will be stored on single user devices that have been encrypted to CUMC IT standards.

Discussions and screening activities will occur in a private area. We do not foresee the recording of research procedures, but if such a situation arises, researchers will be reminded about not using identifying information and cautioned to maintain utmost confidentiality.

Procedures

This study has been designed as a single-blinded, multi-center, randomized clinical trial at New York Presbyterian Hospital Columbia and New York Presbyterian Hospital Cornell. The study population includes all adult neurosurgical procedures for which there exists clinical equipoise performed at each institution over a 4 year and 9-month time period. The treatment variable is the application of topical vancomycin to the surgical site. If a craniotomy is performed, a paste made from vancomycin powder and sterile solution will be applied to the edges and the outer surface of the craniotomy. In all subjects of the treatment group, the powder will be applied directly to the wound prior to the closure of skin or galea. The primary endpoint is the rate of SSI 30 days after the operation. Secondary endpoints include vancomycin levels in serum, CSF, and drain output as well as changes in patient flora collected from the skin and nares preoperatively, 1-2 days postoperatively, 14-30 days post-operatively, and 90 days post-operatively.

All patients who satisfy screening criteria will be approached in the preoperative area by the clinical coordinator.

Informed consent will be obtained and the patient will be randomized to receive topical vancomycin along with the standard of care, or only standard of care. Multiple components of the preparation for surgery, the surgical-site preparation, characteristics of the operating environment, and intraoperative techniques have previously been shown to impact the rate of SSI in neurosurgery. While there are subtle variations in preoperative and intraoperative techniques between attendings and inconsistencies even within a single attending's practice, the variations are small and wound prophylaxis strategies are generally standardized between the two institutions. This is an advantage of including two separate sites that operate under the same hospital policies.

REDCap. The coordinator and the operating team will be unblinded. The patient will remain blinded. The patient may still be excluded from the study if the case is stopped without completion for any reason, if there is no dural closure, or if the protocol is not followed by the operating surgeon for any reason. The circulating nurse will inform the coordinator in the event that it was not followed. The power analysis requires 2,632 patients undergoing craniotomy, craniectomy, and cranioplasty procedures to be enrolled for the primary endpoint but we have accommodated a 2.5% rate of surgeon noncompliance and budgeted 2700 patients total for the entire project. This includes 300 patients who undergo neurosurgical procedures other than craniotomy for whom there is clinical equipoise for the use of topical vancomycin will also be enrolled.

Serum vancomycin levels will be monitored at 6 and 20 hours postoperatively as described in Biological Specimens. When external drains are placed in these patients, vancomycin levels will be monitored in the output fluid. For hemovac and Jackson-Pratt drains, an output will be collected daily and vancomycin levels will be measured by the Irving Center for Clinical Research at Columbia University. In patients where an external ventricular drain is present, additional manipulation and collection may unduly contaminate the device, and lead to infection. Therefore, the drains will be accessed according to standard protocol, which is in the morning on Monday, Wednesday, and Friday or any time the patient becomes febrile.

Subjects will be assessed for the presence of vancomycin-resistant organisms prior to surgery and will be monitored for the emergence of vancomycin-resistant species during follow-up. Baseline, postoperative day 1-2, day 14-30, and day 90 samples will be collected from the nares and future incision site for Staphylococcus aureus and skin flora.
Samples will be collected using pre-moistened culturette rayon-tipped swabs. For the nares, oropharynx and skin swabs, specimens will be incubated in 6% sodium chloride-supplemented tryptic soy broth at 37 °C overnight to enrich for S. aureus growth. Samples will be plated onto mannitol salt agar and incubated at 35 °C for 48 h. Individual positive colonies will be streaked onto sheep blood agar and incubated for an additional 24 h. The Murex StaphAurex rapid latex agglutination test will be used to confirm isolates as S. aureus. Susceptibility testing will be performed by disk diffusion following the method recommended by the Clinical and Laboratory Standards Institute.

Preoperative evaluation including a medical history, physical examination, and routine hematologic and blood chemical testing will be performed. While the patient is in the hospital, the surgical-site and vital signs will be assessed daily.

Existing data directly related to the study aims and outcomes (see attached document) from the patient's medical record will be taken as part of a prospective chart review, and the patient's medical record will be monitored during his or her hospital stay for signs of an adverse event or infection outcomes. A telephone interview will be conducted by a blinded researcher in the period including 2 to 4 weeks and 90 days (+/- 7 days) following the patients' surgeries in order to screen for potential infection-related symptoms and other adverse events. The phone interview script is attached in the study documents. In terms of non-invasive physical measurements, height and weight will be among the demographic data recorded from the patient's medical record to calculate BMI for potential subgroup analyses and associations with infection rates.

Biological Specimens

Description of Specimen and Method of Obtaining:
CSF or other wound drainage may be obtained from study patients for whom a drain is placed as part of clinical care. Specimens may be ordered through the clinical information system, collected by nursing and clinical staff in accordance with standard policy for the drainage type, and sent to the core lab. All fees will be billed to the study. Specimens will be collected in sterile fashion from drainage collection systems in accordance with standard clinical procedure. They will be labeled with a code and the research team has the key and can link specimens to direct identifiers.

Cultures will be collected from skin at incision site and anterior nares preoperatively on the day of surgery, postoperative day 1-2, at 14 and 90-day follow-ups. The coordinator will collect in person for the first three time points. To prevent the need for unnecessary visits, the final two time points will be collected by mail. Patients will leave the hospital with pre- addressed, stamped swab mailers and detailed instruction. De-identified labels will be provided with study identification code.

Blood samples will also be collected from study subjects. Serum levels of vancomycin are analyzed at ~6 and 20 hours postoperatively. Orders are placed for collection in conjunction with routine phlebotomy draws in postoperative craniotomy patients. All fees will be billed to the study.

Specimens will be collected according to hospital policy with multiple unique identifiers and sent to the core lab for analysis. At no point will samples be handled by any member of the study team. Results are obtained through chart review.

Drugs/Biologics

Name:
Vancomycin HCl for Injection USP
Dose: 2g
Study phase:
Phase 3

Manufacturer Information

Name: Mylan Inc.
Address: 1000 Mylan Blvd., Canonsburg, , Canonsburg, United States, 15317, 724-514-1800,
Contact information: (724) 514-1800

Route of administration: Topical
Category: FDA-approved but not used in accordance with the currently approved labeling
Does the Use of the drug/biologic require an Investigational New Drug (IND) or Biological IND (BB-IND) application?
NO – this use is exempt.

21 CFR 312.2(b)(1) criteria met - This is a clinical investigation of a drug product that is lawfully marketed in the United States and all the following apply: (i)The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; and (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

This is a clinical investigation of a drug product that is lawfully marketed in the United States and all the following
apply:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

The drug will be dispensed by the institutional research pharmacy

Analysis of Existing Data and/or Prospective Record Review

Source:
Statewide Planning and Research Cooperative (SPARCS) data system, New York City Vital Records, and New York State Vital Records

The data, documents, or records to be reviewed/abstracted are those to which a member of the research team has legitimate access for non-research purposes (e.g., departmental patient database, physicians' patient clinical

records, student records).

Special authorization is necessary to review the records as the research team does not have access to the data, and a request will be or has been made to access the data.

Source:
Institutional EHR
This data contains direct identifiers (e.g., name, MRN, date of birth)

Future Use

Materials anticipated for future research use:
Data

How data and/or specimens will be retained for future use:
Some or all data and/or specimens, as applicable, will be retained by Columbia researchers for future use.

Intended future use:
Current PI will retain the materials and there is no intent to create a repository or share with other institutional researchers. Information provided in original consent forms will be considered when an addition of future uses is submitted via modification.

What future uses are anticipated?
Data collected from this study will be analyzed throughout and at the completion of this study in order demonstrate our specific aims.

Data/specimen labeling:
Data/specimens will be labeled in the same manner as during collection (e.g., with direct identifiers, coded, de-identified, anonymous).

Physical storage for the specimens/data, including location:
In the same manner as during collection.
The principal investigator and study staff will have access to study data.
Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

Description:
Statewide Planning and Research Cooperative (SPARCS data system)

Plans for release of data and/or specimens:
Only the birth date, name and potentially the UPID of the patients enrolled will be released in order to patient

match within the SPARCS database to receive additional information about the patients pertinent to the study's aims, such as the adverse events and infection status in the 90 days post-operation.

Recruitment And Consent

Screening and/or determining eligibility of prospective subjects:
Patients will be screened using the OR schedule to determine broad eligibility. The patients' medical records will then be used to see if the patients fulfill all inclusion criteria and do not fulfill any exclusion criteria. These actions are allowed through the HIPAA D forms.

Recruitment strategy:
Patients meeting all eligibility criteria and undergoing procedures for which the study offers clear potential benefit in preventing surgical site infection will be introduced to the basic study purpose, procedures, risks, benefits and alternatives in a preoperative consultation by the operating physician or study nurse, either in-office for elective procedures or in- hospital for inpatients. Eligible patients expressing clear interest in participation will be approached in the preoperative area, the same day of their procedure, by the clinical coordinator or other study personnel approved to obtain informed consent after the patient's treating team/attending physician gives their permission for us to approach the patient.

Recruitment Methods:
Person to Person
Flyer/Handout

Informed Consent Process:
Informed consent with written documentation will be obtained from the research participant or appropriate representative. Documentation of informed consent is applicable to the study in its entirety. Documentation of participation will be obtained from adult participants and Legally Authorized Representatives (LARs).

Eligible patients expressing clear interest in participation will be approached in the preoperative area by the clinical coordinator or other study personnel approved to obtain informed consent in writing after the patient's treating team/attending physician gives us permission to approach. Study purpose, procedures, risks, benefits, alternatives and confidentiality will be reviewed in detail, and the subject or legally authorized representative will be given the opportunity to ask questions related to participating in the study.

Subject Language:
Enrollment of non-English speaking subjects is expected.

Languages anticipated:
English
Spanish

Capacity to provide consent:
Those with and/or without capacity to provide their own consent (surrogate consent is anticipated).

Process that will be in place to identify an appropriate surrogate to provide consent:
If the care providers in the procedure described below express any concerns or uncertainty in the patient's capacity for informed consent, the coordinator or other approved consenting researcher will consult them regarding their legally authorized health care proxy. If the appropriate surrogate is available, they will be approached and undergo the usual informed consent process in order to obtain written consent before the subject is eligible to participate and enrolled. If the surrogate is unavailable for whatever reason, the patient will be excluded.

Plan to assess capacity both at the time of enrollment and, if applicable, throughout each subject's participation:
At the time of enrollment, the treating physician or pre-operative area nurse involved in the intake interview will be consulted with regards to the patient's status and capacity to provide informed consent. Throughout the subject's participation, the patient's treating team and electronic medical record will be consulted to assess for any changes in mental status and/or any other barriers to informed continuation of participation.

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):
The purpose is to evaluate topical vancomycin as a means to reduce surgical site infections in neurosurgery. We have four questions we would like to determine (1) determine the effect of the intraoperative application of topical vancomycin to the craniotomy edges and superficial wound in craniotomies on the rate of SSI (2) determine how topical vancomycin applied to the surgical site during craniotomy affects systemic levels, cerebrospinal fluid levels, and wound drainage levels of vancomycin (3) determine how the intraoperative application of topical vancomycin to the surgical site in cranial neurosurgery alters skin flora 10-14 days post-operatively and (4) prospectively

determine which patient and clinical factors predict surgical-site infections in neurosurgical craniotomies. Overall, we would like to a demonstrate the effect of topical vancomycin on the incidence of SSI, drug levels of multiple different body fluids, and the effects of topical vancomycin on the microbiome.

Scientific Abstract:
Surgical-site infections (SSIs) occur in up to 500,000 patients per year in the United States (1-4). Patients with SSIs require significantly longer hospital stays and higher healthcare expenditures. In fact, it is estimated that SSIs are responsible for almost 4 million excess hospital days and billions of dollars in added hospital charges

every year (2,5-7). Additionally, SSIs are a significant source of morbidity and mortality for surgical patients (5,8). Thus, prompt and definitive measures are necessary in order to redress this significant public health concern. Over the past few decades, the implementation of a number of preventative measures—including improved techniques in pre- operative skin antisepsis (4,5) and antibiotic prophylaxis (9-11)—have led to significant reductions in the rate of SSIs. Studies have demonstrated that approximately half of all SSIs are preventable with the proper use of prophylactic antibiotics (5,12). Despite these dramatic improvements, SSIs remain a tremendous burden on the healthcare system. Furthermore, routine use of systemic antibiotic prophylaxis is not without risks, as it may lead to rapid development of antibiotic resistance (13-16), and also exposes patients to undesirable systemic drug effects. The purpose of this study is to evaluate the ability of topical vancomycin to reduce surgical site infections after neurosurgical operations.

Lay Abstract:

In people who have had surgery, infections may occur at or near the part of the body where the operation was performed. These are known as surgical-site infections (SSIs), and in the United States they occur in up to 500,000 patients each year who have had surgery (1-4). Patients with SSIs require longer stays in the hospital and have higher healthcare costs. In fact, it is estimated that SSIs are responsible for almost 4 million excess days spent in the hospital and cost billions of extra dollars every year (2,5-7). SSIs are also a large cause of death and disability for patients who have had surgery (5,8). Therefore, SSIs are a big public health concern, and it is important that steps are taken to reduce the death, disability, cost, and long hospital stays that they cause. Over the past few decades, hospitals have found some ways that have decreased the number of SSIs that occur per year. For example, just before a surgery starts, the doctor cleans the skin with antibiotics (4,5), and can also give antibiotics through an IV depending on the kind of operation (9- 11). Research studies have shown that about one-half of all SSIs can be prevented when antibiotics are given to the patient through an IV (5,12). Despite this big improvement, however, SSIs are still a huge burden on the healthcare system. The other problem is that giving antibiotics can be risky because the patient can be allergic to the drug, may suffer from its side effects, and the drug can lead to growth of antibiotic-resistant bacteria which are harder to treat (13-16). The purpose of this study is to see whether putting topical vancomycin (a type of antibiotic) at the site of surgery will reduce surgical site infections.

Risks, Benefits & Monitoring

Potential Risks:

All potential risks to subject who are willing to participate in the study will be notified of the risks prior to enrollment, and documented on the consent form. Potential risks to the treatment group include an adverse reaction to vancomycin. These allergic reactions to vancomycin are considered very rare and no incidence has been described in prior literature involving topical vancomycin. In literature describing topical application of other antibiotic classes, allergic reactions were mild and localized to site of application. Another potential risk to the treatment group would possibly be promoting vancomycin resistance among native organisms of the patient's microbiome. Given the small amount of vancomycin given, the topical application of the drug, the minimal systemic absorption of topical vancomycin described in other studies, and the fact that this has not been previously described in the literature, this risk is considered to be very low. Another risk is Participation in research may mean a loss of confidentiality. However, all possible measures have been taken in the design of the proposed trial to minimize breaches in confidentiality. There may be unknown risks associated with the study treatment that have not yet been determined by preclinical studies. Patients will be closely monitored for any

unexpected adverse events during the course of the clinical trial, and appropriate care will be administered in the event of any such occurrence. The alternative to enrollment in this trial is to not enroll, in which case the patient will receive the current standard of care for craniotomy patients.

Potential Benefits:

The potential benefits of the research to the patients include a lower rate of surgical site infection. In previous studies of topical vancomycin in other surgical domains, a significantly lower surgical site infection rate as been reported. This study has important implications for future craniotomy patients by investigating a potential intervention to reduce wound infections. Wound infections following craniotomy carry high morbidity and mortality rates, and the risks of the intervention are reasonable compared to the potential benefit of reducing the probability of infection. Topical vancomycin has potential to significantly decrease infection rates in the neurosurgical population, and lead to improved patient outcomes and reduced healthcare costs. In addition, in other studies, topical vancomycin use has been associated with minimal adverse side effects and minimal systemic absorption, and there have been no reports of the emergence of vancomycin resistant organisms.

Alternatives:

An alternative therapy to topical antibiotics in reducing surgical site infections is systemic antibiotics. In comparison to systemic antibiotics, topical antibiotics can achieve much higher local wound concentrations, at the location of potential pathogens, while decreasing the risk of systemic adverse effects. In 1985, Roth et al. emphasized the need for randomized controlled trials to evaluate the efficacy of local antibiotics. Over the past several decades, multiple methods to deliver local antibiotics have been developed and investigated including powders, irrigations, ointments, beads, collagen sponges, and fleece materials. A recent review identified 22 prospective randomized controlled trials over 5 surgical domains, but noted a significant lack of level 1 evidence for many of the topical antibiotics routinely used in practice. Neurosurgical procedures, therefore, provide an opportunity to take advantage of a surgical field that has not yet adapted topical antibiotics without strong evidence but has significant room for improvement in a high SSI rate that is the second most burdensome to the national healthcare system only after SSI associated with cardiothoracic surgery.

Data and Safety Monitoring:

Site PIs will be informed of any adverse events that occur in any enrolled patients, and detailed information regarding these occurrences will be documented and reported to the IRB and DSMB. There will be an external DSMB for this study, composed of 4 members, including a neurosurgeon, a neurologist, an infectious disease doctor, and a biostatistician. DSMBs will convene regularly throughout the duration of the study to adjudicate the designation of the adverse events as due to the study treatment, as well as to reassess the safety of the clinical trial. Furthermore, the DSMB will determine the severity of each AE (i.e Grade 1, Grade 2, Grade 3 or Grade 4) to be documented for the final statistical analysis.

Subjects

Target number of eligible subjects to be included at all sites:

2,632

Anticipated Vulnerable Populations:

Individuals lacking capacity to provide consent
Economically disadvantaged

NCT02284126

Educationally disadvantaged
Non-English speaking

Eligibility:

Inclusion Criteria:

- Adult (18+) neurosurgical procedure (ie.Craniotomy, Craniectomy, and Cranioplasty)

Exclusion Criteria:

- Creatinine > 1.50 mg/dL on admission
- Vancomycin allergy (documented or self-reported)
- Evidence of infection at or near the planned surgical site
- No planned dural or dural-substitute closure
- Spinal instrumentation (topical vancomycin is already standard of care)
- No surface area to apply i.e. Carotid endarterectomy, MRI-guided laser ablation
- Trans-sphenoidal approach
- Acoustic neuroma resection
- Surgeon preference for or against use in the given procedure