Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection: A Multicenter, Randomized, Controlled Trial (VANCO Study)

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Summary: A number of clinical studies in the spine literature suggest that the use of local vancomycin powder may substantially reduce surgical site infections (SSIs). These studies are primarily retrospective and observational and few focus on orthopaedic trauma patients. This study is a phase III, prospective, randomized, clinical trial to assess the efficacy of locally administered vancomycin powder in the prevention of SSI after fracture surgery. The primary goal of the VANCO Study is to compare the proportion of deep SSI 6 months after fracture fixation surgery. A secondary objective is to compare species and antibacterial susceptibilities among study patients who develop SSI. An additional objective is to build and validate a risk prediction model for the development of SSI. The study population consists of patients aged 18–80 years with tibial plateau or pilon (tibial plafond) fractures, at higher risk of infection, and definitively treated with plate and screw fixation. Participants are block randomized (within center) in a 1:1 ratio to either treatment group (local vancomycin powder up to a maximum dose of 1000 mg, placed immediately before wound closure) or control group (standard of care) for each study injury location, and return to the clinic for evaluations at 2 weeks, 3 months, and 6 months after fixation. The targeted sample size for the study is 500 fractures per study arm. This study should provide important information regarding the use of local vancomycin powder during the definitive treatment of lower extremity fractures and has the potential to significantly reduce the incidence of infection after orthopaedic trauma.

Key Words: vancomycin powder, local antibiotics, surgical site infection, biofilm, tibial plateau fractures, tibial pilon fractures

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BACKGROUND AND RATIONALE

Local antibiotics offer several theoretical advantages over systemic antibiotics for the prevention of surgical site infection (SSI) after orthopaedic trauma surgery. Although intravenous (IV) antibiotics are routinely given at the time of fixation surgery and have been shown to be efficacious,[1–4] potential disadvantages can be associated with this mode of delivery. Systemic antibiotics are delivered to areas of the body where they are not needed, limiting the concentration at the surgical site at the cost of reducing the risk of systemic toxicity. The ability to achieve higher concentrations with local antibiotics may help ensure that the minimum inhibitory concentration of specific pathogens is exceeded with a comfortable margin, thus contributing to greater efficiency in the prevention of biofilm formation and its impact on implant-related SSI after orthopaedic trauma.[5] Furthermore, IV antibiotics can only be delivered to tissues with sufficient blood supply, but this pathway may be compromised in acutely injured tissues. These limitations, coupled with high rates of SSI in certain fracture surgeries, have prompted surgeons to consider local antibiotic administration to reduce SSI risk.

Ideally, the local antibiotic delivery device would not only be effective in preventing infection but also be low cost, not take up space in the wound, not cause drainage at the wound site, and be able to protect the entire surgical wound from infection.[6] Antibiotic beads can make wound closure difficult and may require subsequent removal[7–9] when space is limited. In addition, some dissolvable antibiotic beads have been reported to cause drainage at the wound site.[10] One proposed solution to these concerns is the use of vancomycin powder applied directly into the wound bed at the time of wound closure.

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Several clinical studies in the spine literature describe the use of local vancomycin powder to reduce SSI. These studies are limited by their retrospective nature and selection bias; however, they demonstrated a few clinically important phenomena including (1) deep infections were 4 times as likely in patients who did not receive the local vancomycin powder prophylaxis[11–17]; (2) complications or side effects associated with local use of vancomycin were rare[13–17]; and (3) costs of care were reduced.[18] There is little published clinical data on the use of vancomycin powder in orthopaedic trauma patients[19] and no level I evidence on this topic.

Vancomycin has been chosen as the local antibiotic for this study mainly because of its established track record in the spine[14–17] and because of its efficacy against the most common pathogens in orthopaedic trauma patients, particularly methicillin-resistant *Staphylococcus aureus* and other gram positive bacteria (eg, methicillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci).[20–22] In addition, there are limited concerns regarding inhibition of bone healing or osteogenic cytotoxicity,[23] nephrotoxicity, or other systemic toxicity associated with vancomycin, especially at relatively lower doses.[15]

Although there is great interest in the use of local antibiotics to reduce risk of infection after fracture fixation surgery, to date, the hypothesis that vancomycin powder will reduce SSI in orthopaedic fracture patients has not been rigorously tested.

METHODS: TRIAL DESIGN, PARTICIPANTS, AND INTERVENTION

This study is a phase III, prospective, randomized, clinical trial to assess the efficacy of locally administered vancomycin powder in the prevention of SSIs after definitive fixation for a tibial plateau or pilon (plafond) fracture. The primary goal of the VANCO Study is to compare the proportion of deep SSIs within 6 months in patients treated with local vancomycin powder with those treated without local vancomycin powder. A secondary objective of the study is to compare species and antibacterial susceptibilities of the bacteria in study patients who develop SSIs between those treated with and without local vancomycin powder. An additional objective is to build and validate a risk prediction model for the development of SSIs in patients treated without local vancomycin powder and then to explore whether local vancomycin powder modifies the predicted risk of infection.

The study was initiated at 34 US trauma centers participating in the Major Extremity Research Consortium (METRC).[24] The list of participating centers can be found at the end of this article. Vancomycin is a Food and Drug Administration (FDA) approved drug. However, the method used to administer the drug for this study (applying the powder over the implant and soft tissue at the time of wound closure) is considered an "off-label" use, thus requiring an investigational new drug (IND) approval from the FDA (IND no.119891 received 31 October 2013). The study protocol, including the written informed consent form, was approved by the Johns Hopkins Bloomberg School of Public Health (location of the METRC Coordinating Center, the MCC), the Department of Defense Human Research Protection Office (DoD HRPO, study sponsor), and the local institutional review board (IRB) at each participating center. Furthermore, each site was required to obtain DoD HRPO approval of local IRB documents and certification by the Coordinating Center to ensure proper training on study procedures and data collection before initiation of the study.

Participants

The study population consists of patients aged 18–80 years with tibial plateau or pilon (tibial plafond) fractures at a high risk of infections (defined below) that are definitively treated with plate and screw fixation. High risk fractures are defined as those injuries meeting at least one of the following conditions: (1) treated definitively in a delayed fashion with external fixation and definitive treatment more than 3 days after injury once the swelling has resolved adequately; (2) Gustilo type I, II, and IIIA[25,26] open fracture, regardless of timing of definitive treatment; or (3) associated with ipsilateral leg compartment syndrome treated with fasciotomy wound(s), regardless of timing of definitive treatment.[27] These 3 situations are all thought to be associated with increased infection rate based on existing literature. It should be noted that patients who are initially treated with an external fixator for reasons other than swelling and the high-energy nature of the fracture (such as temporizing until an orthopaedic trauma surgeon is available) are not eligible, as these lower energy injuries are not thought to be associated with a high risk of infection. Detailed inclusion and exclusion criteria are summarized in Table 1.

As this study strives to be a pragmatic trial, patients are not excluded based on having other fractures, potential risk factors for infection, infections at sites other than the study injury, traumatic brain injury, spinal cord injuries, or the presence of immunosuppression. Furthermore, patients are not disqualified when treated initially with a temporary external fixator or have a portion of the fixation before definitive plate fixation, at any initial surgery before randomization. The study injury for patients with multiple qualifying injuries is defined as the injury with the highest probability of becoming infected in the opinion of the treating surgeon. If permitted by the local site IRB, patients in the VANCO Study can be concurrently enrolled in other METRC and non-METRC studies.

Participants meeting the study criteria described below are approached for informed consent in the hospital before definitive fixation. METRC has adopted a comprehensive informed consent process for all of its studies that involves the treating surgeon, the clinical site research coordinator, and materials and resources to facilitate patients and family members making an informed decision about participation. Details of this process are described in **Supplemental Digital Content 1** (**see Figure**, http://links.lww.com/BOT/A874). A legally authorized representative is permitted to consent on behalf of patients who are unable to do so before definitive fixation. All screened and enrolled patients have inclusion and exclusion criteria documented in REDCap,[28] the web-based, distributed data collection system used for all METRC studies. Enrolled patients are prospectively followed for 6 months after definitive fixation.

Intervention

The surgical technique is to place 1000 mg of sterile vancomycin powder directly in the wound over all

TABLE 1. Inclusion and Exclusion Criteria for the VANCO Study

Inclusion Criteria	Exclusion Criteria
1. Patients aged 18–80 yrs 2. Injury meeting the following criteria: a. Tibial plateau or tibial pilon fractures b. Treated operatively with plate and screw fixation c. The nature of the fracture suggests it is at high risk of infection, as indicated by one or more of the following: i. Treated definitively in a delayed fashion, with initial treatment using an external fixator and definitive treatment more than 3 d later to allow swelling to resolve adequately ii. Gustilo Type I, II, and IIIA open fractures iii. Associated with ipsilateral leg compartment syndrome treated with fasciotomy wound(s)	1. Study injury fractures that are already infected at time of study enrollment 2. Type IIIB or IIIC open fractures 3. Patients who have already had definitive fixation before enrollment in the study 4. Patients with an allergy, drug administration reaction, or other sensitivities to vancomycin (such as a history of Redman's Syndrome) 5. Patients who are currently pregnant 6. Patients who speak neither English nor Spanish 7. Patients who are incarcerated 8. Patients who are determined by the local researchers at the site to have severe problems maintaining follow-up for such reason as: a. Diagnosed with a severe psychiatric condition b. Intellectually challenged without adequate family support c. Living outside the hospital's catchment area and no method of follow-up d. Planning to follow-up at another medical center not participating in the study e. Being homeless without adequate contact information to follow-up

metal implants (plates and screws) at the time of wound closure.[14–17] It is thought that application of powder over the plate in this manner creates a "kill zone" for bacteria that inhibits biofilm formation. When multiple wounds are present with multiple plates, the surgeon splits the dose of powder between those wounds according to his or her's clinical judgment. The powder is not put into small percutaneous incisions used to place single screws.

Surgeons have been trained to have the vancomycin powder make as much contact with the plate as possible while also allowing vancomycin powder to be placed into the surrounding surgical wound. When definitive fixation is performed as a staged procedure, vancomycin powder is only used during the procedure that is thought to have the highest risk of SSI, which typically is the final procedure. To minimize variation across sites, surgeons are instructed to use the powder form of the drug for the purposes of this study and not to create a paste for delivering the vancomycin; they should spread the drug into the wound bed.

It is unknown how long the antibiotics must be present in the wound to be clinically effective, but data from the spine literature has shown this delivery method to be efficacious. From the perspective of preventing the development of bacterial resistance, it is thought that a high dose over a short period is preferable to lower doses over a longer period, as would be seen when antibiotics are mixed with longer acting carriers. As there is no carrier for the antibiotics, the vancomycin powder is likely to be fully absorbed within a day or even less time.[15]

Most orthopaedic trauma surgeons are already familiar with using sterile vancomycin powder in the operating room to make antibiotic beads and nails. The powder is delivered in a sterile form, and hospitals are already familiar with the storage, handling, and management of the drug. In extremity wounds, a typical local dose would be 1000 mg of vancomycin powder placed into the wound at the time of closure. Previous data indicate that the systemic load from this amount is likely to be very low[14–17] and undetectable in the systemic circulation in one previous study in spine surgery.[15] The typical IV dose is at least 1000 mg twice daily (often for 6 or more weeks if the patient has an infection). It is clear then that a single local dose is a relatively small amount of the drug compared with what is typically used in systemic IV therapy.

Vancomycin can be given as IV prophylaxis if that is the center's standard of care approach or if it is appropriate for a given patient. The risk of renal (or other) toxicity from simultaneous IV and local vancomycin powder application is extremely unlikely based on previous data demonstrating low systemic absorption.[14–17] In current clinical practice, much larger doses of local vancomycin powder are placed in beads repeatedly during serial irrigation and debridements while patients receive IV vancomycin for weeks at a time without any known negative consequence.[29] Whatever antibiotic prophylaxis protocol is used at the METRC center, participating institutions have been instructed to apply it consistently across the treatment and control groups. Investigators agreed to not change IV prophylaxis choice based on which treatment group the patient is assigned, and this is tracked carefully for compliance. Surgeons are allowed to use antibiotic beads that may contain vancomycin in the small subset of open fractures that receive multiple debridements. However, any removable local antibiotic delivery devices used during earlier surgeries must be removed before final closure at the time of definitive treatment, regardless of the study group to which the patient is assigned.

Control Group (Standard of Care)

Participants in this group receive standard of care treatment. and are not to receive local vancomycin or any other antibiotic powder at any time for treating the study injury.

The risks of giving antibiotic powder are increased for participants who have a known allergy or who are susceptible to local toxicity to the drug. Otherwise, risks of participation in this study are those typical of the inherent risks for the operative procedures involved and do not differ from the standard of care.

Crossover from one treatment arm to another should be rare and should only occur if the surgical team determines the

local vancomycin powder placement is not feasible, if vancomycin powder is not available, or if an investigator forgets to place the local vancomycin powder in the wound of a patient randomized to the treatment group or inadvertently places it in a patient who has been assigned to the control group. Patients are blinded to the treatment group to which they are assigned, leaving no chance that they will elect to switch groups based on the outcome of the randomization.

With the exception of the provision of local vancomycin powder for those assigned to the treatment arm, both groups otherwise receive standard of care, including prophylactic IV antibiotics. Minor variability in practice is allowed at the discretion of the operating surgeon. Patients are block randomized (within center) in a 1:1 ratio to either treatment group (local vancomycin powder) or control group (standard of care) for each study injury location (tibial plateau or pilon). The block sizes are randomly permuted and are not disclosed to sites.

METHODS: OUTCOME MEASURES AND DATA COLLECTION

Frequency and Duration of Follow-up

Data collection for the VANCO Study includes recording details regarding the patient's medical history, injury attributes, and treatment characteristics at the index hospitalization. Using the final definitive fixation date as the basis for creating follow-up visit windows, participants are expected to return to the clinic for evaluations at 2 weeks, 3 months, and 6 months after fixation. At each follow-up visit, participants undergo a clinical evaluation by the treating surgeon and are interviewed by the research coordinator. The data collected at each timepoint are summarized in **Supplemental Digital Content 2** (**see Table**, http://links.lww.com/BOT/A877).

Clinical assessments include data collection pertaining to complications (type, severity, and treatment), fracture healing, wound healing, pain, details regarding antimicrobial therapy, and a comprehensive assessment of evidence of infection (when applicable). Patient interviews focus on tracking rehospitalization events to monitor for complications that have occurred since the previous clinical evaluation. At 6 months, several patient-reported outcome measures are also collected. These include the Brief Pain Inventory,[30] health-related quality of life using the Veterans RAND 12-Item Health Survey (VR-12),[31] the Short Musculoskeletal Function Assessment,[32] and an assessment of the patient's return to usual major activities. The use of standardized outcome measures as part of METRC studies has been described previously elsewhere.[33]

Blood sampling is performed according to standard clinical care practice at each institution. This typically includes pregnancy tests when appropriate, serum creatinine, and complete blood count at baseline. In addition, for the first 30 patients assigned to the treatment arm at the lead clinical site (where the IND approval was awarded, the University of Maryland, Baltimore, MD), vancomycin levels and other laboratory results were collected within 24 hours of placement of the antibiotic powder in the operating room. The Coordinating Center does not provide the vials of vancomycin powder to clinical sites and so to comply with the FDA annual reporting requirements, the name, strength, manufacturer, and batch number for every vial of vancomycin used in this study are recorded.

Primary Outcome

The main outcome measure is the presence of a deep SSI in the first 6 months after surgery, as determined by the treating orthopaedic surgeon using Centers for Disease Control and Prevention guidelines.[34–36] The Centers for Disease Control and Prevention guidelines were developed to provide clear, objective criteria for evaluating surgical wounds and determining the presence or absence of infection. The current guidelines define deep infections after fracture fixation as those occurring within 90 days,[37] whereas previous guidelines have referred to a timeframe of a year. Each of these timepoints (except the 1 year timepoint) is being tracked in this study, but the final follow-up visit is scheduled at 6 months because 85% of the infections are known to present by this timepoint in this study population.[21] A central adjudication committee that is blinded to treatment assignment will adjudicate all primary outcomes.

Wound characteristics are also being evaluated using the ASEPSIS method.[38–41] In this system, wounds are scored using the weighted sum of points assigned for predetermined criteria including the need for **A**dditional treatment, presence of **S**erous drainage, **E**rythema, **P**urulent exudates, **S**eparation of deep tissues, the **I**solation of bacteria, and the duration of patients **S**tay (ASEPSIS). This system of wound scoring complements the CDC guidelines. For each patient determined to have an infection, treatment details are also recorded. For the purpose of this study, deep infections are defined as those requiring operative treatment, whereas superficial infections are those treated nonsurgically.

Secondary Outcomes

The secondary outcome measure of the VANCO Study pertains to bacterial speciation and sensitivities. Routine clinical practice for all deep SSIs includes the collection of sterile intraoperative wound cultures. In addition to bacterial speciation, both the susceptibilities and antibiotic resistance for identified pathogens are determined as part of routine practice. Comparisons will be made across treatment groups.

Monitoring and Quality Assurance

Details of the METRC-wide standard operative procedures for monitoring can be found in **Supplemental Digital Content** 3 (**see Figure**, http://links.lww.com/BOT/A875). The monitoring plan is designed to verify site compliance with the protocol and study-specific standard operative procedures on the data collection and procedures. The plan facilitates compliance with good clinical practice guidelines (5.18.1). An independent data safety monitoring board reviews study progress, all reported complications, and serious adverse events during meetings held twice per year. The chair of the data safety monitoring board serves as the medical monitor, who reviews each serious adverse event as it is reported in real-time.

METHODS: DATA MANAGEMENT AND ANALYSIS

Data Management

Site research coordinators and clinical investigators collect data using paper case report forms designed specifically for this study and then enter that data into REDCap. Details about data handling and data management can be found in **Supplemental Digital Content 4** (**see Figure**, http://links.lww.com/BOT/A876).

Data Analysis and Sample Size

Statistical analyses will be performed according to the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized. Treatment effects for binary outcomes will be estimated using a 2-group comparison of proportions; 95% confidence intervals for the absolute risk difference and relative risk will be reported. Tests on the null hypothesis of no treatment effect will be conducted and *P* values will be reported.

Newly developed statistical procedures that leverage baseline covariates will be used to increase statistical precision (ie, power).[42] Regression modeling may be used if concerns about confounding arise because of unexpected imbalances between treatment groups with respect to key prognostic baseline factors. Hierarchical modeling may also be used if concerns regarding the clustering of outcomes within centers emerge. Information may also be borrowed from the control group of the METRC OXYGEN Study (which has a similar patient population and outcome variables and is running concurrently at METRC sites) if concerns about power arise because of event rates being lower than anticipated.

Multiple imputation will be used to address missing baseline covariates. Missing outcomes will not be imputed. Sensitivity analyses will be conducted to evaluate the robustness of the trial results to various untestable assumptions about the missing outcome mechanism.

For patients who are infected, a one-sided, 95% lower confidence interval for the difference in antibiotic sensitivity between the treatment and control arms will be computed. This difference will be compared with a 10% noninferiority margin.

In previous work,[43] an infection risk prediction model for orthopaedic trauma surgery was developed. Data from the control group of the VANCO Study will be used to validate this model. The predictive accuracy of the model will be assessed by computing the estimated risk of infection for each control patient and comparing it to actual infection rates using standard metrics (sensitivity, specificity, and area under the receiver operating characteristic curve). Using data from control patients, an attempt will be made to improve the prediction model using logistic regression and machine learning techniques.

The sample size is based on a 2-group comparison of proportion of deep SSI between the treatment groups during the first 6 months of treatment. In a previous study, 235 fractures drawn from a similar patient population as that proposed yielded a 3-month deep infection risk of 11.5%.[44] Rates of deep SSI after these fractures have varied considerably in previous studies with both higher and lower rates being reported in what are typically retrospective studies. To calculate the sample size, it was assumed that patients in the control arm would have an infection probability of 11%. Using a 2-sided 0.05-level test of no treatment difference, 464 patients are needed to have 80% power to detect a 5.1% absolute reduction (45% relative reduction) in the probability of infection by 6 months. One interim analysis will be performed (after a third of the patients have been followed for 6 months) using an O'Brien–Fleming stopping boundary. The sample size is inflated by 1% to preserve the overall type I error. The sample size is further conservatively inflated by 5% to account for loss to follow-up. Based on these considerations, the targeted sample size for the study is 500 fractures per study arm.

DISCUSSION

This is the first large multicenter, randomized, controlled trial evaluating the efficacy of locally administered vancomycin powder in an extremity trauma patient population. There are several major strengths associated with this study. First, the randomized design of this study should provide a definitive answer to scientific question addressed by the primary aim. The study is both rigorous in design and adequately powered to answer the clinical questions it poses. In addition, this study draws on patients treated at multiple level 1 trauma centers across the United States, so the results should have strong generalizability given the representativeness of the enrolled patients and the facilities that treat these injuries.

Another advantage of this study is its pragmatic and simple implementation approach. Patient enrollment criteria are minimal, simple, and most clinical care is provided with surgeon discretion for the treatment of such injuries. The study requires little training on the study drug or its method of delivery and site investigators are well versed in the use of vancomycin in treating similar injuries. In addition, vancomycin powder is inexpensive (<$10/dose) compared with the analogous expenses associated with newer emerging treatment aimed at reducing SSI. Furthermore, surgeons, hospitals, and operating room personnel are already familiar with vancomycin powder, so there are few clinical barriers to acceptance if the technique's effectiveness is demonstrated.

The chief potential limitation of this study is associated with the measurement of the primary outcome, SSI. The diagnosis of an infection rests directly with the treating surgeon who is not blinded to treatment, thus creating the potential for bias. The decision to unblind the treating surgeon was made for 2 reasons. First, ethical concerns prohibit the use of a powder containing no antibiotics because a placebo of this type represents a foreign body, which might actually increase the infection rate. Second, having a surgeon other than the treating surgeon evaluate wounds and make treatment decisions (or perhaps even come into the operating room to place the powder and close the wound) was deemed impractical and outside of the current practices at existing centers.

There are several study qualities that limit the potential for bias of the surgeon being unblinded to treatment. First, detailed standardized data are collected about infections and their characteristics. This information is used to centrally adjudicate all deep infections in a blinded fashion. Furthermore, superficial SSIs are not included as primary outcomes, as these, in theory, may be more prone to surgeon bias. Obvious postoperative purulent wound drainage is difficult for a surgeon to ignore and the indications for surgical management are relatively clear.[5] The diagnosis of a superficial SSI is much more subjective, which likely means it would be more prone to subtle bias. Thus, despite a reduced event rate and need for larger sample size, only deep SSIs are included as a primary outcome.

This study, with its rigorous methodology, should provide important and clinically convincing information regarding the use of local vancomycin powder during the definitive treatment of lower extremity fractures. Vancomycin powder is a low cost and readily available antibiotic already familiar to orthopaedic trauma surgeons. If positive, the results of this randomized trial have the potential to significantly reduce the incidence of infection after orthopaedic trauma by introducing only a minor change in established practice.

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