

Does prophylactic local tobramycin injection lower open fracture infection rates?

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Abstract

Objective: To determine whether local aqueous tobramycin injection in combination with systemic perioperative IV antibiotic prophylaxis will reduce the rate of fracture-related infection (FRI) after open fracture fixation.

Other Outcomes of Interest: (1) To compare fracture nonunion rates and report differences between treatment and control groups and (2) compare bacterial speciation and antibiotic sensitivity among groups that develop FRI.

Design: Phase 3 prospective, randomized clinical trial.

Setting: Two level 1 trauma centers.

Participants: Six hundred subjects (300 in study/tobramycin group and 300 in control/standard practice group) will be enrolled and assigned to the study group or control group using a randomization table. Patients with open extremity fractures that receive definitive internal surgical fixation will be considered.

Intervention: Aqueous local tobramycin will be injected into the wound cavity (down to bone) after debridement, irrigation, and fixation, following closure.

Main Outcome Measurements: Outcomes will look at the presence or absence of FRI, the rate of fracture nonunion, and determine speciation of gram-negative and Staph bacteria in each group with a FRI.

Results: Not applicable.

Conclusion: The proposed work will determine whether local tobramycin delivery plus perioperative standard antibiotic synergism will minimize the occurrence of open extremity FRI.

Level of Evidence: Level 1.

Keywords: local antibiotics, fracture-related infection, surgical site infection, tobramycin, open extremity fracture

1. Introduction

Fracture-related infections (FRIs) are a significant cause of disability among military and civilian personnel who have sustained an open fracture.^[1] Combat-associated open extremity injuries often occur because of a high-energy blast mechanism. They are defined as fractures with soft tissue trauma that results in direct communication

between the outside environment and the fracture.^[2] These injuries are at a higher risk for infection and nonunion than closed fractures because of local contamination, damage of the soft tissue envelope, and impaired bone vascularity, resulting in compromised bone healing and diminished host defenses against bacteria.^[3] In the United States, closed fractures treated with implants have an infection rate of 0.5%–2.5%, while open fractures have a much higher infection rate, with a 6%–16% rate of infection in all open fractures.^[4–14] Infections are common after combat-related injuries, affecting up to 34% of patients with extremity injuries.^[15] Military personnel are at the greatest risk for FRI secondary to open extremity fracture (OEF), with rates reported as high as 77% for tibia injuries among combat casualties.^[1,16,17] These injuries, in turn, are associated with significant resource utilization and, more importantly, increased patient morbidity including reoperations and late amputations.^[18–20]

OEF treatment aims to promote fracture healing and restore function while preventing the development of infection. The current gold standard treatment is immediate prophylactic antibiotic administration and tetanus update, urgent wound debridement and irrigation, fracture stabilization, perioperative and postoperative systemic antimicrobial therapy, and judicious wound closure based on cleanliness.^[21] Early prophylactic systemic antibiotics lower infection rates in open fractures but have limitations in achieving adequate concentration at the hypoperfused wound area.^[22] The limited vascularity secondary to soft tissue disruption often seen in

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OEF leads to insufficient systemic antibiotic concentrations in tissues of interest. In addition, if systemic antibiotic concentrations are increased to achieve minimum inhibitory concentration for pathogens at the wound, there is heightened concern for systemic drug toxicity. In sharp contrast, locally administered antibiotics achieve high drug concentration directly within the wound cavity with minimal systemic side effects.^[2,3] Local antibiotic therapy has been shown to reduce FRI rates in combat and civilian injuries.^[1,2,3] Considering the severe implications of postoperative infections in OEF, it is imperative that all measures, specifically the use of local prophylactic antibiotics, be investigated.

The most commonly used local antibiotic delivery carrier in orthopaedics is polymethylmethacrylate (PMMA) cement.^[2,4] Tobramycin-impregnated PMMA beads have demonstrated promising results in open fractures but require a secondary procedure for removal because of the nonresorbable nature of the carrier.^[2,5,26] Another disadvantage is that PMMA is not biodegradable and can serve as a nidus for infection once the eluted antibiotic concentration is below minimum inhibitory concentration. There are several resorbable carriers available, such as calcium sulfate and calcium phosphate.^[2,7] However, the cost of these products, lack of structural support, lack of prospective clinical evidence, and drainage associated with resorption are major drawbacks.^[2,4] Efforts initiated in spine surgery have shifted to using vancomycin powder applied directly to the surgical wound with positive results.^[2,8–31] These same efforts are being replicated in the field of orthopaedic trauma.

The Major Extremity Trauma and Research Consortium (METRC) Vancomycin (VANCO) and Tobramycin (TOBRA) research studies are assessing the efficacy of local powdered antibiotics in the prevention of surgical site infection for at-risk open or closed tibial plateau and plafond fractures after surgery. We will use local tobramycin injection in an aqueous form in all OEF fixation patients. By including all OEF, our study demonstrates greater applicability and is more generalizable to community and military wounds.

Multiple animal models have demonstrated the synergistic effect of systemic cephalosporin and local aminoglycoside administration in reducing OEF infection and osteomyelitis. The completed VANCO and the ongoing TOBRA trials assess the efficacy of locally administered vancomycin powder alone and in combination with tobramycin powder in civilian patients who have undergone operative management of high infection risk lower-extremity fractures. However, the limitation of those studies is to focus solely on the lower extremities and exclude Gustilo type IIIB and IIIC fractures. Thus, we propose a pragmatic, prospective randomized controlled trial (RCT) evaluating the efficacy of local tobramycin adjunct to standard of care (SOC) in all OEF fixation patients. The primary aim of this study is to compare the rates of FRI 1 year after open fracture fixation surgery. Other aims of interest are to report on and compare nonunion rates between groups, with an additional objective comparing the bacterial speciation and antibiotic sensitivity among study subjects who develop FRI.

This phase 3 study will take place at 2 high volume, level 1 accredited trauma hospitals. Each hospital admits more than 3500 adult patients with trauma per year with more than 1400 high-level trauma activations. From 2018 to 2019, the orthopaedic trauma service at each site treated more than 200 OEFs. This study consists of patients aged 18–80 years with open fractures requiring orthopaedic implant fixation. Injuries of interest are proximal to the carpal bones for the upper extremity and distal to the pelvis for the lower extremity. Participants will be block randomized by unblinded research personnel into either treatment group (local aqueous tobramycin injection 2 mg/mL after fixation and wound

closure plus SOC) or control group and evaluated in the clinic at 2 and 6 weeks and 3, 6, and 12 months after definitive fixation. The targeted sample size is 600 patients with 300 per study arm. The overarching objective of this study is to investigate the efficacy of local aqueous tobramycin injections in reducing FRI after definitive treatment of OEFs in military and civilian personnel.

2. Methods: Trial Design, Participants, and Intervention

2.1. Design

This phase 3 prospective randomized clinical trial will test the efficacy of local aqueous tobramycin injection in preventing FRI for all OEF fixations. The goal is to promote improved patient outcomes by decreasing the rate of FRI without negatively affecting bone union. In addition, bacterial speciation and resistance will be performed to learn more about the microbial etiology of FRI. All aspects of the study will be in concordance with the International Consensus Recommendations for Musculoskeletal Infection.^[32] This study will be conducted after Institutional Review Board approval for the 2 collaborating level 1 trauma centers is acquired.

2.2. Participants

This study consists of patients with an OEF who receive surgical fixation: open reduction internal fixation with plate and screws and/or intramedullary nail. All OEF fixation patients, aged 18–80 years, with open upper-extremity and/or lower-extremity fractures, and severe high-energy injuries that require plastic coverage or vascular repair (Gustilo type IIIB and IIIC injuries), are included. In attempt at a pragmatic approach, patients will not be excluded based on multiple fractures, temporary external fixation, serial surgical management, traumatic brain injury, spinal cord injuries, or immunosuppression. Patients treated with resorbable local antibiotic drug delivery devices will be excluded because of wound drainage leading to false-positive FRI diagnosis and additional antibiotic administration. In addition, patients who receive formal debridement and irrigation 48 hours beyond OEF will also be excluded. More detailed inclusion and exclusion criteria can be found in Table 1.

Because this is a pragmatic study that compares the use of local aqueous tobramycin with the SOC, patients treated with antibiotic-impregnated PMMA beads/spacer in the small subset of open fractures that receive them will not be excluded. Patients who receive staged Masquelet treatment for segmental bone defects will be included in the study, and definitive treatment will occur at the time of bone grafting. As performed by Lawing et al, Gustilo-Anderson type IIIB and IIIC will be incorporated into this study.

Potential study participants will be identified by members of the research team in the emergency department or the preoperative holding area, and written informed consent will be obtained. Throughout the informed consent process and at every subsequent study visit, patients will be encouraged to ask questions about the study or study procedure. The subject will be reminded that they may withdraw from participation at any time and the steps to take in the event of an adverse reaction. Participants will be followed for 1 year after definitive treatment.

2.3. Ethics Approval and Informed Consent

The University of Kentucky Institutional Review Board will act as the single site overseeing the University of Kentucky and

TABLE 1**Inclusion and Exclusion Criteria.**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Patient age: 18–80 years | Patient younger than 18 or older than 80 years |
| OEF that meet the following criteria: | Patients who already had definitive fixation before enrollment |
| Surgically treated with an orthopaedic implant (plates and screws and/or intramedullary nail) | Patients with an allergy to tobramycin |
| Fracture proximal to carpal bones for upper extremity | Known prior infection (systemic or at injury site) |
| Fracture distal to pelvis for lower extremity | Patients treated with resorbable antibiotic carrier |
| | Operative treatment delayed >48 hours after injury |
| | Patients who are pregnant |
| | Patients who do not speak English nor Spanish |
| | Patients with insufficient follow-up |
| | Death |
| | Amputation to avoid reconstruction or amputation for necrosis without infection |
| | No follow-up after initial discharge |
| | Patients whom the local researcher deems to have problems maintaining follow-up for the various reasons |
| | Incarcerated |
| | Intellectually challenged without adequate family/social support |
| | Diagnosis of severe psychiatric condition |
| | Planned follow-up at another medical center not participating in this study |
| | Homeless without adequate contact information for follow-up |

Vanderbilt University, with approval being acquired before enrollment. Written informed consent will be collected from every participant before enrollment (Protocol number: 65241; PI name: A.A.). This is reflected in our methods under the subsections “design” and “participants.”

2.4. Intervention

2.4.1 Tobramycin Injection. In the treatment arm, a validated and safe dosage of 80 mg of tobramycin diluted in 40 mL of normal saline (2 mg/mL) will be locally injected.^[23] This dosage has been proven safe and without adverse effects on bone union. It has also demonstrated no systemic side effects in a retrospective clinical study with open fractures.^[23] Systemic levels are undetectable 24 hours after delivery, while concentrations within the wound cavity remain bactericidal for 14 days.^[33,34] Local tobramycin will be injected into the wound cavity (down to bone) after irrigation, debridement, fixation, and following final wound closure at the time of definitive treatment. In wounds that remain open or undergo serial debridement, tobramycin will be injected during each subsequent debridement until hardware implantation and wound closure.

Regarding the development of bacterial resistance, it is believed that a local high antibiotic concentration over a short period is preferable to the converse of low-dose antibiotic exposure over an extended period.^[35] Unfortunately, the latter

situation is routinely created when using local drug delivery with PMMA and theoretically can lead to a higher rate of bacterial resistance.^[35] This will be obviated in this study with a direct aqueous antibiotic injection which will likely be fully absorbed within a day or less.^[29] Further advantages of using aqueous tobramycin injection include ease of implementation and, compared with vancomycin, lower cost and increased accessibility.^[36]

2.4.2. Standard of Care. SOC will be provided alongside the administration of systemic IV antibiotics as soon as possible after OEF injury. OEF will urgently undergo formal debridement and irrigation, followed by provisional or definitive treatment. Prophylactic IV antibiotics will be continued during the perioperative care period per hospital protocol. The selection of IV antibiotics is determined from an agreed-upon protocol that is consistent between both participating institutes.

Patients will be randomly assigned to the treatment group or control (SOC) group using a randomization table created by our team biostatistician. Subjects will be block randomized to ensure that the allotment of patients with open fractures who require plastic coverage or vascular repair is similar for both study groups. Randomization will be concealed to the treating surgeon and patient. The creation and testing of the randomization module will be overseen before initiation of the study at both sites by the study team’s biostatistician. Because patients are blinded, it is improbable that they will elect to switch groups based on assignment. Patients who have sustained multiple open fractures will be assigned to either control or treatment group as a whole and not by individual fracture.

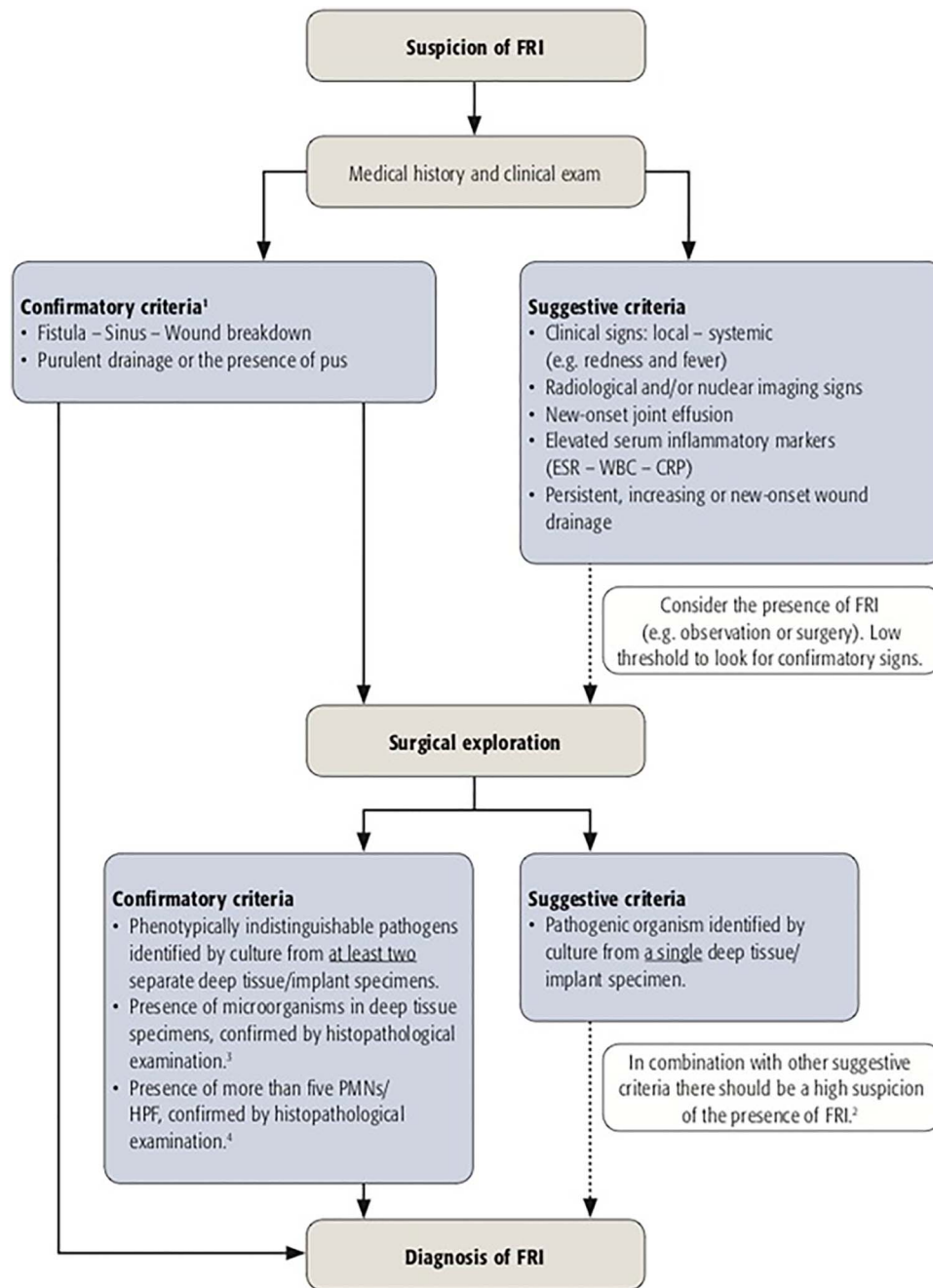
If selected to the treatment group, all open fractures sustained by the individual will be treated with the intervention to eliminate surgeon bias to treatment. Furthermore, the treating surgeon will select the study fracture as the injury with the highest probability of becoming infected, as proposed by O’Toole et al in the VANCO trial. The designated study fracture will be followed for study outcomes.

3. Methods: Outcome Measures and Data Collection

3.1. Frequency and Duration of Follow-up

After enrollment and treatment, patients will be followed during their hospital course. The surgeon will assess their wounds during their inpatient stay and routine clinic follow-up appointments (at 2 and 6 weeks and 3, 6, and 12 months). A flowchart detailing study activities is given in Table 2. Radiographs will also be obtained postoperatively and during clinic follow-up. Nonunion status will be assessed using the modified Radiographic Union Score for Tibial fractures score, combined with clinical observation of functional weight-bearing pain.^[37,38] Patients who have a reoperation to attain bone union will be considered a nonunion. For patients who suffer from FRI, bacterial speciation and antibiotic sensitivity will be determined using sterile intraoperative cultures.

Orthopaedic trauma follow-up compliance is a concern, especially at the 1-year mark. Follow-up rates at 1 year have been reported as low as 29%, with only 67% of patients attending their first scheduled appointment.^[39,40] However, these studies do not consider follow-up rates when patients are monetarily incentivized. Accordingly, both participating institutes have a final follow-up of enrolled patients of ≥90% with METRC funded studies that pay patients per visit. Per Madden et al,^[41] adult patients with trauma with open fractures have



¹ In cases of purulent drainage or fistula/sinus/wound breakdown, the presence of pathogens identified by culture is not an absolute requirement (e.g. in the case of chronic antibiotic suppression).

² If the positive culture is from sonication fluid, it is highly likely that FRI is present. This is especially true when virulent bacteria (i.e. *Staphylococcus aureus*) are present.

³ The presence of microorganisms is confirmed by using specific staining techniques for bacteria and fungi.

⁴ The presence of an average of more than five PMNs/HPF on histopathological examination should only be considered diagnostic of FRI in chronic/late-onset cases (e.g. fracture nonunion).

ESR: erythrocyte sedimentation rate, WBC: white blood cell count, CRP: C-reactive protein, PMN(s): polymorphonuclear neutrophil(s), HPF: high-power field.

Figure 1. Descriptive flowchart to diagnose FRI. The figure is reprinted from Govaert et al^[42] under the terms of the Creative Common License. No modifications were made to the material.

a 6.7% loss to follow-up. To promote follow-up, patients will be contacted by phone both 1 week and 1 day before their study visits. They will be compensated \$100 for attending each clinic visit (\$500 total compensation if all 5 study visits are attended).

Blood sampling and specimen collection will be performed according to each institute's respective protocols. The tests include, but are not limited to, complete blood count, bacterial cultures, serum creatinine, and pregnancy tests.

TABLE 2
Flowchart of Study Activities.

| Procedures | Inpatient | | Outpatient | | | | |
|----------------------------|-----------|----------------------|------------|--------|---------|---------|----------|
| | Screen | Postoperative course | 2 week | 6 week | 3 month | 6 month | 12 month |
| Inclusion/exclusion review | X | | | | | | |
| Informed consent | X | | | | | | |
| Wound assessment | | X | X | X | X | X | X |
| Nonunion assessment | | | | | X | X | X |

3.2. Primary Outcome

The primary outcome will be the presence or absence of FRI in the first year after surgery, as defined by the FRI consensus group.^[42,43] At each follow-up visit, patients will be assessed for suggestive and confirmatory criteria for FRI, as presented in Figure 1, and for superficial infection, according to Mangram et al.^[44] Their wounds will be closely monitored while in the hospital and when they return to the clinic. One year was chosen as the final follow-up visit because >98% of infections are known to present by this time.^[45] A central adjudication committee blinded to treatment will adjudicate the primary outcome of FRI when under dispute. Superficial infections, as defined by the Center for Disease Control criteria,^[44] that respond to antibiotic therapy (not requiring surgery) will be recorded and analyzed separately from FRI. In a secondary analysis, regression models will be performed during final data analysis to adjust for injury variables such as type I/II/III, B, and C open fractures; upper-extremity and lower-extremity injuries; and interventions such as Masquelet technique, vascular repair, or those treated with PMMA. Comparison between primary and secondary analysis FRI rates will provide insight into which variables, if any affect FRI.

Patients will be evaluated by the surgeon and interviewed by research personnel during their follow-up visits. Data collected will include patient age, sex, medical history, injury location, mechanism of injury, treatment of injury, date of injury, smoking status, illicit drug use, presence of diabetes, presence of polytrauma (2 or more long bone injuries with involvement of 2 or more systems), American Society of Anesthesiologist score, time from injury to antibiotic, time to surgical procedure, number of surgical procedures, type of fixation, time to wound coverage/closure, and duration of time to the latest follow-up. The open fractures will be classified according to the Gustilo-Anderson^[46] and Orthopaedic Trauma Association Open Fracture Classification.^[47]

3.3. Other Outcome of Interest

Of interest, we will compare rates of fracture nonunion and report any differences between the treatment group and the control group. The surgeon will be responsible for assessing union status using the modified Radiographic Union Score for Tibial fracture score combined with clinical observation of functional weight-bearing pain.^[37,38] According to this system, scores are based on the presence or absence of fracture line and bridging on the anteroposterior and lateral radiographic views of the fracture.^[37] A central adjudication committee that is blinded to treatment will adjudicate the outcome of fracture nonunion when under dispute. Patients who have a surgery to attain union will be considered a nonunion. Fractures clinically diagnosed as nonunion within 1 year of surgical fixation will be classified as nonunion. Surgical intervention to promote fracture union does not have to occur within 1 year, but the indication for surgery must be made within

this period. The surgeons and adjudication committee will use a combination of these methods to determine nonunion status. The authors understand the limited applicability of each method individually, leading to the combined method discussed.

Finally, another outcome of interest will determine the speciation and antibiotic sensitivity of gram-negative and gram-positive staphylococcal species in each patient with an FRI because these are the pathogens commonly associated with OEF.^[48] SOC entails that all patients with FRI return to the operating room for sterile intraoperative wound cultures to determine causative organism(s) and antibiotic sensitivity. In addition, comparisons between bacterial speciation and antibiotic resistance data from both groups will be made.

3.4. Monitoring and Quality Assurance

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected. Monitoring will ensure that the reported trial data are accurate, complete, and verifiable and that the conduct of the trial follows the currently approved protocol/amendment(s) with International Conference on Harmonization Good Clinical Practice and with applicable regulatory requirement(s). There will be an independent clinical monitor for this study.

3.5. Data Analysis and Sample Size

For this study, 600 subjects will be enrolled, approximately half at each participating medical center over a 3-year study period. The final fourth year is needed to collect 1-year follow-up data on all study participants. In total, there will be 300 in the treatment group and 300 in the control group. Both participating institutions have a final follow-up of enrolled patients of $\geq 90\%$, and according to Madden et al,^[41] adult patients with trauma have a 6.7% loss to follow-up rate in a large orthopaedic trauma RCT. Therefore, a 15% loss to follow-up rate is very conservative, demonstrating appropriate safeguard mechanisms in place. After accounting for our estimated potential loss to follow-up (15%), this leaves us with approximately 255 subjects per group. All sample size calculations and power analyses were performed based on at least 255 subjects per group to account for potential loss to follow-up. Power analyses considered the power to detect between-group difference in proportions using a one-sided continuity corrected 2-group X^2 with $\alpha = 0.05$ and are summarized below. Treatment effects for binary outcomes will be estimated using 95% confidence intervals for the relative risk and the absolute risk difference, which will be reported. Comparing the infected and noninfected patients, risk factors for FRI and nonunion in OEF after surgical fixation will also be determined. Risk factors affecting primary and other outcomes will be investigated using logistic regression. Although site effects are unlikely, we will use logistic regression in a secondary analysis to adjust for each aim's site or risk factor effects.

Calculations used to determine the appropriate sample size for the primary objective are based on rates from Lawing et al. They reported an FRI rate of 14% in the control group and 6% in the treatment group, necessitating 211 patients per group (total 422) to detect a surgical site infection rate difference between the 2 groups, assuming 80% power when alpha is 0.05. The same test will be used at all-time intervals of 2 and 6 weeks and 3, 6, and 12 months.

4. Discussion

This multicenter, prospective RCT provides a novel perspective on the treatment of patients with extremity trauma. We seek to evaluate local tobramycin use on FRI, nonunion rates, and bacterial speciation and resistance. This study's design incorporates several inherent strengths. This study is both rigorous in design and adequately powered to answer the proposed clinical question. In addition, both participating level 1 trauma centers have agreed on a congruent protocol, rendering potentially more effective and manageable oversight.

Our pragmatic approach paralleled with ease of treatment implementation suggests applicability to combat and civilian wound management. Another advantage incorporates the limited and concise nature of our patient inclusion and exclusion criteria. In addition, this study requires little training considering the simplicity of the intervention. In addition, the tested antibiotic tobramycin is cost-effective and readily available. All of these considered, there are very few clinical barriers to implementation if efficacy is demonstrated.

Potential limitations to this study include patient enrollment, loss to follow-up at 1 year, wound severity variables, the subjectivity of superficial infections, insufficient sample size to determine difference in nonunion status between groups, and no growth FRI. If recruitment becomes insufficient, we will expand the study to include another level 1 trauma center with appropriate capabilities to begin enrollment. When dealing with wound severity, factors such as the timing of flap coverage and ischemia time are well known to contribute to FRI development.^[49,50] Nonetheless, in such an event, regression models will be performed to assess injury factors that are predictive of FRI for severe OEF with plastic coverage or vascular repair. Similarly, regression models will also be performed to include injury variables that affect FRI, such as type I/II/III/IV, B, and C open fractures and upper-extremity and lower-extremity injuries. Superficial infections are not included in the primary outcome because of the subjective nature of diagnoses, making it prone to bias. Despite the lower rates of superficial infection necessitating a larger sample size, only FRI is included in our primary outcome. This study is funded and powered for the primary aim of FRI and is not adequately powered for changes in the nonunion rate.

For cases of union ambiguity, nonunion will be further defined as a need for secondary bone grafting or need for surgical intervention as reported by Bhandari et al in the Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial shaft fracture trial and O'Toole et al in the VANCO trial.^[35,51] If the decision to return to the operating room is made within 1 year of their definitive procedure for any bone grafting or repeat surgery to promote fracture union, then the fracture will be classified as nonunion. Finally, in an attempt to mitigate no growth cultures for FRI, research personnel will keep strict records on preoperative and postoperative antibiotic administration through patient drug diary and electronic medical record review. Treating surgeons will also be educated on strict adherence to SOC principles of not administering

antibiotics before obtaining cultures during FRI debridement/treatment unless the patient is in septic shock.

In conclusion, if significant, this study's application and ease of implementation should provide innovative strategies for extremity wound management. The proposed practice requires minimal alteration to the current SOC and is familiar to practicing orthopedists. Applying local aqueous tobramycin injections could reduce upper-extremity and lower-extremity infection rates for both military and civilian personnel. If successful, it will improve our knowledge of OEF management to prevent the devastating and frequent morbidity associated with FRI.

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