Contemporary Clinical Trials xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Topical vancomycin to reduce surgical-site infections in neurosurgery: Study protocol for a multi-center, randomized controlled trial

Alexander J. Jonokuchi[a], Jared Knopman[b], Ryan E. Radwanski[a,*], Moises A. Martinez[a], Blake Eaton Samuel Taylor[a], Michael Rothbaum[b], Sean Sullivan[c], Trae R. Robison[a], Eric Lo[a], Brandon R. Christophe[a], Eliza M. Bruce[a], Sabrina Khan[c], Christopher P. Kellner[a], Dimitri Sigounas[b], Brett Youngerman[a], Emilia Bagiella[d], Peter D. Angevine[a], Franklin D. Lowy[c], E. Sander Connolly[a]

[a] Department of Neurological Surgery, Columbia University College of Physicians and Surgeons, 710 W 168th Street, New York, NY 10032, United States
[b] Department of Neurological Surgery, Weill Cornell Medical Center, 525 East 68th Street, Box 99, New York, NY 10065, United States
[c] Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, 630 W 168th Street, New York, NY 10032, United States
[d] Center for Biostatistics, Department of Population Health Science & Policy, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029, United States

ARTICLE INFO

Keywords:
Vancomycin
Topical administration
Craniotomy
Wound prophylaxis
Surgical site infection
Neurosurgery

ABSTRACT

Surgical-site infections (SSIs) account for 20% of all healthcare-associated infections, are the most common nosocomial infection among surgical patients, and are a focus of quality improvement initiatives. Despite implementation of many quality care measures (e.g. prophylactic antibiotics), SSIs remain a significant cause of morbidity, mortality, and economic burden, particularly in the field of neurosurgery. Topical vancomycin is increasingly utilized in instrumented spinal and cardiothoracic procedures, where it has been shown to reduce the risk of SSIs. However, a randomized controlled trial assessing its efficacy in the general neurosurgical population has yet to be done.

The principle aim of "Topical Vancomycin for Neurosurgery Wound Prophylaxis" (NCT02284126) is to determine whether prophylactic, topical vancomycin reduces the risk of SSIs in the adult neurosurgical population. This prospective, multicenter, patient-blinded, randomized controlled trial will enroll patients to receive the standard of care plus topical vancomycin, or the standard of care alone. The primary endpoint of this study is a SSI by postoperative day (POD) 30. Patients must be over 18 years of age. Patients are excluded for renal insufficiency, vancomycin allergy, and some ineligible procedures. Univariate analysis and logistic regression will determine the effect of topical vancomycin on SSIs at 30 days.

A randomized controlled trial is needed to determine the efficacy of this treatment. Results of this trial are expected to directly influence the standard of care and prevention of SSIs in neurosurgical patients.

1. Introduction

1.1. Background and rational

Surgical-site infections (SSIs) are the most common nosocomial infection among surgical patients, and they complicate up to 500,000 surgeries annually in the U.S. [1–3]. In addition to causing substantial morbidity and mortality, SSIs are also a focus for quality improvement initiatives, as they account for 1 million excess days of hospitalization and $1.6 billion in additional healthcare expenditure [1,4–7]. They are also a major cause of unplanned 30-day hospital readmission, the rate of which affects hospital reimbursement as part of new U.S. healthcare policies [6,8,9].

In neurosurgery, SSIs complicate 2–5% of approximately 2 million procedures annually, [4,7,10–13] triple the length of stay (LOS), and on average cost an additional $26,000 per case [1]. The incidence of SSIs in neurosurgery overall varies from 1 to 11% depending on factors including: type of procedure, demographic characteristics (e.g. older

* Corresponding author.
E-mail addresses: Alexander.Jonokuchi@downstate.edu (A.J. Jonokuchi), jak9030@med.cornell.edu (J. Knopman), rer246@cornell.edu (R.E. Radwanski), mm4512@cumc.columbia.edu (M.A. Martinez), mir2033@med.cornell.edu (M. Rothbaum), ss4009@cumc.columbia.edu (S. Sullivan), trr2116@cumc.columbia.edu (T.R. Robison), yl3294@cumc.columbia.edu (E. Lo), brc2119@cumc.columbia.edu (B.R. Christophe), sk3782@cumc.columbia.edu (S. Khan), christopher.kellner@mountsinai.org (C.P. Kellner), bey2103@cumc.columbia.edu (B. Youngerman), emilia.bagiella@mountsinai.org (E. Bagiella), pda9@cumc.columbia.edu (P.D. Angevine), fdl189@cumc.columbia.edu (F.D. Lowy), esc5@cumc.columbia.edu (E. Sander Connolly).

http://dx.doi.org/10.1016/j.cct.2017.10.004
Received 31 May 2017; Received in revised form 23 September 2017; Accepted 4 October 2017

age), comorbidities (e.g. uncontrolled diabetes), presence of hardware, procedure duration, length of stay (LOS), and presence of postoperative cerebrospinal fluid (CSF) leaks [14–18].

Over the past several decades, many preventative measures have been implemented such as improved techniques in preoperative skin antisepsis [19], however, SSIs remain a tremendous burden on the healthcare system.

Intravenous prophylactic antibiotics have variable delivery to the surgical site, which limits their ability to achieve bactericidal concentrations locally, and come with the risk of systemic adverse effects, including hypersensitivity reactions and renal toxicity [20]. Topical antibiotics, by contrast, have the advantage of achieving high local concentrations at the surgical site, where contaminating pathogens are located, while minimizing systemic toxicity. Due to the increasing prevalence of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA), which now accounts for as many as half of all SSIs [21], it is not surprising that the efficacy of topical vancomycin for reducing SSIs is being increasingly explored [22]. Notably, topical vancomycin is now commonly used in patients undergoing instrumented spine procedures, where it has been shown to reduce the incidence of SSIs from 4.7 to 0.7% [23–27]. A similar benefit was demonstrated in cardiothoracic surgery when vancomycin paste was applied to the cut edges of the sternum during sternotomy closure [28,29].

To our knowledge, there is currently no data assessing the efficacy of topical vancomycin among neurosurgical patients undergoing craniotomy or non-instrumented spinal procedures, and a prospective, randomized clinical trial is needed.

S. aureus colonizes the anterior nares and skin in more than a third of hospitalized patients, of which 1–5% are MRSA, and colonization on admission is associated with an increased risk of postoperative *S. aureus* infections [30,31]. In fact, data from neurosurgical patients suggest that those identified with MRSA colonization may benefit from specific perioperative care with vancomycin [32]. In addition to assessing SSI rates, microbiology data collected in parallel may provide valuable information regarding patient risk and the effects of topical vancomycin on a patient's natural skin microbiology.

2. Methods: participants, interventions, and outcomes

2.1. Study setting

This study is conducted in two large, New York City healthcare centers in the United States of America. The patient population varies widely in socioeconomic status, race/ethnicity, age, and residency. Columbia University Medical Center is the lead center responsible for ensuring compliance and providing training to other participating centers.

2.2. Eligibility criteria

Adult neurosurgical patients undergoing cranial or non-instrumented spinal procedures are eligible for the trial. Exclusion criteria include patients with renal insufficiency (creatinine > 1.5 mg/dL), allergy to vancomycin, and instrumented spinal procedures (see Table 2 for a full list of inclusion and exclusion criteria). Patients undergoing instrumented spinal procedures are excluded from the trial as topical vancomycin is already indicated in this patient population [23–27]. Pediatric patients (under age 18) are excluded due to insufficient data available for adults to judge the potential risk of topical vancomycin in children. Additionally, pediatric neurosurgical procedures are performed in associated, yet separate hospitals. Due to known adverse effects of vancomycin, patients are not included in the study if they have evidence of renal insufficiency that is either documented or noted on admission (serum creatinine > 1.5 mg/dL). Similarly, patients who report an allergy to vancomycin, including dermatological manifestations (e.g. hives, Red man syndrome, or other rashes), dizziness, or subjective hearing loss are excluded. Only up to 300 non-craniotomy cases will be included in the study.

Additionally, acoustic neuroma cases are excluded due to potential ototoxic effects and resection proximity to the vestibulocochlear nerve (VIII). Other neurosurgical procedures excluded are carotid endarterectomies, which confer a significantly lower risk of SSIs, and transsphenoidal approaches, where bacterial flora differs considerably. Same-day discharges (e.g. microdiscectomies) are excluded, as there is insufficient time to monitor serum vancomycin levels postoperatively. Due to studying the efficacy of topical vancomycin as prophylaxis, rather than treatment, patients with a known infection adjacent to the operative site (e.g. subdural empyema) are also excluded. Chronic and acute concurrent diseases are documented for each subject and maybe used later in analysis, but preoperative medical status will not be used to exclude subjects unless they violate the aforementioned exclusion criteria.

2.3. Intervention

Current standard perioperative care for all subjects involves intravenous administration of cefazolin approximately 1 h prior to incision, unless the patient reports a significant allergy to cephalosporins or penicillin, in which case intravenous vancomycin is given. Routinely, surgeons may ask patients to shower with an antiseptic agent, such as chlorhexidine, the day prior to surgery [33]. In the OR, the surgical site is shaven using electric clippers, disinfected with povidone-iodine and chlorhexidine, and draped per standard protocol. No other topical antibiotics are applied into the incisional site outside of this stated antibiotic usage. Postoperative care follows the standards set by the Columbia University Department of Neurological Surgery. All patients will be continued on IV fluids and medications if they are unable to take PO. The wound will be examined 4–6 h after surgery and the patients will be transferred from the post anesthesia care unit (PACU) to the neurological surgery post-op floor or to the neurologic intensive care unit (NICU) according to the patient's acuity level. For patients transferred to floor, indwelling urinary catheters will be immediately discontinued if urine output is appropriate. Patients transferred to the NICU will have urinary catheters removed on post-operative day 2 (POD2). Drains will only be used when deemed necessary by the attending surgeon. Dressings are typically removed on POD 1 for single level spine procedures, while they are removed on POD 2 for craniotomies and larger spine cases.

For all subjects randomized to the treatment group, 1 g of commercially available topical vancomycin powder, pre-packaged in a sterile vial, is applied directly to the surgical site during wound closure. Among patients undergoing a craniotomy, a paste is also prepared by mixing an additional 1 g of vancomycin powder with 1 mL of sterile saline solution (Tis-U-Sol®), which is then applied to all free bone flap edges prior to flap reattachment as well as to incisional skin edges prior to galeal closure. The paste is prepared by the OR scrub nurse immediately prior to application and the operating surgeon administers all treatment. For cases only involving a burr hole, the paste is applied to the bone edges around the defect.

Upon wound closure, the operating surgeon is asked whether the protocol was followed correctly. The response is documented by the circulating nurse and maintained with the patient's study record. Subjects may be secondarily excluded if, for any reason, the case is stopped without completion or the protocol is not followed. Treatment is administered in addition to the standard of care; patients randomized to the control arm only receive the standard of care treatment alone. The surgeon has the right to discontinue designated treatment drug if it violates any patient safety. Vancomycin serum level labs are ordered once surgeon is aware that the subject has been randomized to the treatment arm and has consented to the study. Although the study drug is used once, a follow-up phone call is made 14–30 days from discharge in order to monitor patient's health. Patient is not allowed to participate