Title: Topical Vancomycin for Neurosurgery Wound Prophylaxis
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Structured Abstract

Purpose:
This study evaluated the ability of topical vancomycin to reduce surgical site infections (SSIs) after neurosurgical operations. It also assessed systemic levels of vancomycin following topical application, changes in postoperative skin flora, and patient characteristics that impact rates of SSI.

Scope:
Postoperative SSIs in neurosurgical patients carry a significant risk of increased morbidity and mortality. With SSIs accounting for approximately 20% of nosocomial infections and costing approximately $1.6 billion annually, there is a need for additional prophylaxis to improve current standards of care. Topical vancomycin is increasingly utilized in instrumented spinal and cardiothoracic procedures, for which it has been shown to reduce the risk of SSIs.

Methods:
This prospective, multicenter, patient-blinded, randomized controlled trial enrolled 973 patients over 5 years. Serum vancomycin levels within 24 hours following surgery were recorded, and microbiology cultures from anterior nares and skin were collected preoperatively (on the surgery day) and postoperatively on days 1-2. Phone interviews were conducted between days 14 and 30 after surgery to assess infections, wound recovery, and adverse events.

Results:
The topical vancomycin treatment group comprised 484 patients (973 total enrolled patients), The authors found no significant association between preoperative *S. aureus* colonization and postoperative colonization. There is minimal systemic absorption of topical vancomycin, no significant difference in AEs or hearing changes, and no increase in methicillin- or vancomycin-resistant microorganisms We conclude that topical vancomycin treatment is safe in the setting of neurological surgery.

Key Words: topical vancomycin; neurosurgery; surgical site infection; antibiotics; wound prophylaxis

Purpose

The purpose of this study is to evaluate topical vancomycin as a means to reduce surgical site infections in neurosurgery. We have four questions we would like to address: (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 postoperatively; and (4) prospectively determine which patient and clinical factors predict surgical site infections in neurosurgical craniotomies. Overall, we would like to demonstrate the effect of topical vancomycin on the incidence of SSI, identify the drug levels of multiple different body fluids, and demonstrate the effects of topical vancomycin on the microbiome.

Scope

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 preoperative 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 a 1.37% rate of MRSA-associated infection. Extrapolating to the full national population, there were 585,000 craniotomies and 14,040 postoperative infections. Published series report the rate of infection in intracranial neurosurgery at a 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; 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, more 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.

This study has been designed as a single-blinded, multicenter, 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.

Methods

Study Design and Setting

This study is a prospective, multicenter, randomized, patient-blinded, two-armed clinical trial conducted at NewYork Presbyterian Columbia University Irving Medical Center (CUIMC) and NewYork Presbyterian Weill Cornell Medical Center (WCMC).

Eligibility Criteria

Adult patients (>18 years) undergoing cranial or non-instrumented spinal procedures were eligible for the trial. Exclusion criteria include renal insufficiency (creatinine >1.5 mg/dL), allergy to vancomycin, vestibular schwannoma cases, carotid endarterectomies, transsphenoidal cases, known infection adjacent to the operative site, and same-day discharges. Chronic and acute concurrent diseases were documented for each subject but were not used as exclusion criteria. Patients undergoing instrumented spinal procedures were excluded from the trial, as topical vancomycin is already indicated for this population.

Randomization

After screening and obtaining consent, eligible patients were randomized in a 1-to-1 ratio through the Research Electronic Data Capture (REDCap), a secure, Web-based data management system. Patients were randomized to receive either standard prophylaxis or topical vancomycin at the surgical site in addition to standard prophylaxis. Standard prophylaxis includes intravenous cefazolin 1 hour prior to incision. Attending surgeons could elect to use intravenous vancomycin as standard prophylaxis for patients randomized to the control arm with a cephalosporin or penicillin allergy; otherwise, patients in the control arm received no topical or intravenous vancomycin.

Intervention

In the OR, the surgical site was shaven using electric clippers, disinfected with povidone-iodine and chlorhexidine, and draped per standard protocol. Postoperative care followed the standards set by the Columbia University Department of Neurological Surgery. All patients were continued on IV fluids and medications if they were unable to take PO. The wound was examined 4-6 hours after surgery, and the patients were transferred from the post-anesthesia care unit 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 the floor, indwelling urinary catheters were immediately discontinued if urine output was appropriate. Patients transferred to the NICU had urinary catheters removed on postoperative day 2 (POD 2). Drains were only used when deemed necessary by the attending surgeon. Dressings were typically removed on POD 1 for single-level spine procedures, and they were removed on POD 2 for craniotomies and larger spine cases.

For all patients randomized to the treatment group, 1 g of commercially available topical vancomycin powder, pre-packaged in a sterile vial, was applied directly to the surgical site during wound closure. Among craniotomy patients, a paste was also prepared by mixing an additional 1 g of vancomycin powder with 1 mL of sterile saline solution (Tis-U-Sol), which was 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 was prepared by the OR scrub nurse immediately prior

to application, and the operating surgeon administered all treatment. For cases only involving a burr hole, the paste was applied to the bone edges around the defect.

Patients could be secondarily excluded if, for any reason, the case was stopped without completion or the protocol was not followed. The operating surgeon had the right to discontinue the designated treatment drug if it violated any patient safety. Vancomycin serum level labs were ordered after the surgeon was aware that the subject had been randomized to the treatment arm and had consented to the study.

Outcomes

The primary outcome was a surgical site infection (SSI) by postoperative day (POD) 30. As defined by the Centers for Disease Control and Prevention (CDC) criteria, a SSI may be superficial, deep, or in organ space. Infections above the galea were considered superficial, those between the dura and galea were considered deep, and those intradural (e.g., meningitis) were considered organ space. The secondary outcomes were (1) the degree of systematic exposure, by measuring serum vancomycin levels drawn at 6 and 24 h postoperatively, and (2) the incidence of possible adverse effects of vancomycin (e.g., rash, dizziness, and sensorineural hearing loss), by screening at follow-up. At follow-up, patients were asked if they have experienced tinnitus, diminished hearing, or sensation of fullness in their ear following surgery. Positive reports of the aforementioned, not previously noted in preoperative evaluation or self-reported as pre-existing, were qualifying adverse events. Any exacerbation of preoperative hearing changes was reported as an adverse event as well.

In addition, we monitored for changes in the antibiotic susceptibility profiles of microbial flora (namely, *S. aureus*) from swabs taken both preoperatively and during follow-up. Finally, secondary outcomes included length of stay, length of intensive care, rate of re-operation, functional outcomes, and mortality.

Follow-Up

Postoperative follow-up primarily consisted of a telephone interview conducted between POD 14-30 ± 7 days by trained research staff or the clinical coordinator. Using a comprehensive checklist, patients were screened for signs and symptoms of infection, including fever or chills; increased pain; redness, swelling or warmth around the surgical site; and drainage fluid, discharge, or pus from the incision. In addition, patients were screened for adverse events, including hearing loss and local or systemic allergic reactions. If either an infection or an adverse event of any kind was suspected per checklist criteria, the site coordinator reported this information to the principal investigator, who then informed the patient's neurosurgeon and other relevant healthcare providers for appropriate medical evaluation.

At the time of telephone interview, patients were reminded to mail in their swabs. If contact with the patient was not accomplished initially, repeat attempts were made later that same day and during subsequent days to call the patient or relatives. In addition to maintaining close contact with residents and attending physicians who were involved in the patients' care, we also screened for SSIs by reviewing patient EMRs and generating reports of International Classification of Disease, Ninth Revision (ICD-9) codes consistent with SSIs. Suspected SSIs were inspected and classified by a blinded investigator.

Serum Analysis

To monitor for systemic absorption of topical vancomycin, serum vancomycin levels were drawn at 6 and 24 h after wound closure. Serum levels were measured among patients in the treatment group as well as those who receive intravenous vancomycin as standard of care, regardless of randomization. An “undetectable” vancomycin level was defined as ≤3.0 mg/dL (Columbia) and ≤3.5 mg/dL (Weill Cornell).

Microbiology Analyses

Microbial cultures were obtained from the anterior nares and surgical site preoperatively before draping and standard skin preparation protocols, within 48 hours of wound closure, and again at 2 weeks and 3 months following surgery with premoistened culturette rayon-tipped swabs (Becton Dickinson). Patient mailers were used to obtain 2-week and 3-month swabs remotely. Cultures were initially stored at 4°C and later were incubated in 6% sodium chloride–supplemented tryptic soy broth at 37°C overnight to support *S. aureus* growth. The samples were then plated on mannitol salt agar (Becton Dickinson), which selected for *Staphylococcal* species for 48 hours at 35°C. Colonies of *S. aureus* that altered mannitol agar from pink to yellow were then streaked onto sheep blood agar and incubated for 24 hours. The presence of *S. aureus* was then fully ascertained using the Murex StaphAurex rapid latex agglutination test (Remel).

Vancomycin susceptibility testing was completed using Etest, and DNA sequencing was utilized to identify known genes of resistance. Genotyping of the variable-repeat region of protein A (*spa*) gene was used to determine clonal lineage of *S. aureus*, and *spa* types were assigned using StaphType software (version 2.2.1, Ridom).

Statistical Analyses

An intention-to-treat analysis was used in addition to an analysis that compared patients who actually received vancomycin to those who did not. At each time point, cases that were lost to follow-up were dropped from all further outcome analysis. If the sample size and power of the study became too small as a result of excluding patients with missing data, an extreme case analysis was performed in which patients who were assigned to the placebo group would be given a favorable designation and patients in the treatment group, an unfavorable designation. A standard univariate analysis was then performed, using Pearson’s chi-squared test for categorical variables and Student’s t-test for continuous variables as appropriate. Means and standard deviations were calculated for continuous variables, and contingency tables were used for discrete and dichotomous variables. A multivariate logistic regression model determined the effect of topical vancomycin on SSIs at POD 30.

Similar statistical analyses were performed to assess secondary outcomes, safety outcomes, adverse events, and results of microbiological studies. Frequency of detectable serum vancomycin was assessed between patients who received topical vancomycin without intravenous vancomycin and those who received intravenous vancomycin alone (positive control) using a standard contingency table comparison. The means and standard deviations were calculated for serum vancomycin concentration among those with detectable values and compared positive control patients who received intravenous vancomycin using the Student t-test. Microbiology cultures were evaluated based on frequency of pre- and postoperative *S. aureus* colonization of the anterior nares and skin, and the treatment and control groups were compared. Differences in colonization according to race/ethnicity and frequency of methicillin-resistant *S. aureus* (MRSA) colonization were compared by contingency table analysis. For mortality rate, a 30-day mortality table estimated by the Kaplan-Meier method was constructed.

Results

Final data analysis, including incorporation of supplemental data from the Statewide Planning and Research Cooperative System (SPARCS) dataset, is ongoing. In total, 973 patients were enrolled, including 484 in the treatment group and 489 in the control group. Five hundred fifty-six (57.1%) patients were women, and the mean age was 54 years of age.

We observed only ~2% patients treated with topical vancomycin who exhibited slightly positive vancomycin serum levels compared with those who received intravenous vancomycin. The difference in serum vancomycin levels was not significantly different; however, the frequency at which systemic absorption was observed suggests that topical vancomycin has minimal systemic effect.

There was no observed difference between the treatment and control groups in the likelihood of persistence of preoperative colonization of the nares or skin. Similarly, there was no observed difference between the treatment and control groups in the likelihood of de novo postoperative colonization of the nares or skin. Based solely on this data, no evidence was found for selectively using prophylactic, topical vancomycin based *on S. aureus* colonization patterns.

There was no significant difference in the incidence of surgical site infections between the treatment and control groups.

Our study supports the use of topical vancomycin in cranial and un-instrumented spine neurosurgery. There is minimal systemic absorption, no significant difference in AEs or hearing changes, and no increase in methicillin- or vancomycin-resistant microorganisms. Additionally, topical vancomycin does not appear to significantly change *S. aureus* colonization patterns. We conclude that topical vancomycin treatment is safe in the setting of neurological surgery.

List of Publications and Products

1. Jonokuchi AJ, Knopman J, Radwanski RE, et al. Topical vancomycin to reduce surgical-site infections in neurosurgery: Study protocol for a multi-center, randomized controlled trial. *Contemporary Clinical Trials*. 2018;64:195-200. doi:10.1016/j.cct.2017.10.004

2. Radwanski RE, Christophe BR, Pucci JU, et al. Topical vancomycin for neurosurgery wound prophylaxis: an interim report of a randomized clinical trial on drug safety in a diverse neurosurgical population. *Journal of Neurosurgery*. 2019;131(6):1966-1973. doi:10.3171/2018.6.JNS172500

3. Ruan DT, Ulene S, Christophe B, Clarke A, Connolly E. Evaluating Topical Vancomycin to Reduce Surgical-Site Infections in Craniotomies: Interim Analysis of a Randomized Controlled Trial. San Diego, CA; April 13–17, 2019. 2019 AANS Annual Scientific Meeting. J Neurosurg. 2019;131(1):2-116. doi:10.3171/2019.7.JNS.AANS2019abstracts