Reducing surgical site infections following craniotomy: examination of the use of topical vancomycin

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OBJECT Although the use of topical vancomycin has been shown to be safe and effective for reducing postoperative infection rates in patients after spine surgery, its use in cranial wounds has not been studied systematically. The authors hypothesized that topical vancomycin, applied in powder form directly to the subgaleal space during closure, would reduce cranial wound infection rates.

METHODS A cohort of 150 consecutive patients who underwent craniotomy was studied retrospectively. Seventy-five patients received 1 g of vancomycin powder applied in the subgaleal space at the time of closure. This group was compared with 75 matched-control patients who were accrued over the same time interval and did not receive vancomycin. The primary outcome measure was the presence of surgical site infection within 3 months. Secondary outcome measures included tissue pH from a subgaleal drain and vancomycin levels from the subgaleal space and serum.

RESULTS Vancomycin was associated with significantly fewer surgical site infections (1 of 75) than was standard antibiotic prophylaxis alone (5 of 75; p < 0.05). Cultures were positive for typical skin flora species. As expected, local measured vancomycin concentrations peaked immediately after surgery (mean ± SD 499 ± 37 µg/ml) and gradually decreased over 12 hours. Vancomycin in the circulating serum remained undetectable. Subgaleal topical vancomycin was associated with a lower incidence of surgical site infections after craniotomy. The authors attribute this reduction in the infection rate to local vancomycin concentrations well above the minimum inhibitory concentration for antimicrobial efficacy.

CONCLUSIONS Topical vancomycin is safe and effective for reducing surgical site infections after craniotomy. These data support the need for a prospective randomized examination of topical vancomycin in the setting of cranial surgery.


KEY WORDS vancomycin; surgical site infection; craniotomy; postoperative infection

Surgical site infections (SSIs) are a significant source of morbidity and mortality. The costs associated with treating SSIs are estimated to be as high as $3 billion per year and more than $20,000 per case.9 Methods for improving patient outcomes in a cost-effective manner are needed as rising health care expenses outpace national resources and insurers threaten to deny coverage for iatrogenic infections.

The application of topical antibiotics (i.e., antimicrobial compounds) directly into a surgical wound is a safe and effective method for reducing SSI after spinal surgery.2,3,8,10,11 Sweet et al.18 reported a 2.4% reduction in the rate of SSI with the addition of topical vancomycin after elective spine surgery. The most common pathogens, Staphylococcus aureus and S. epidermidis, are skin flora thought to be inoculated directly into the wound during surgery. These species are increasingly resistant to the cephalosporins used for routine preoperative prophylaxis.
Despite encouraging results from human and animal studies, the use of topical antibiotics during cranial surgery has not been studied systematically. Topical vancomycin has the potential to reduce infection rates after craniotomy when used as an adjunct to routine intravenous prophylaxis and proper surgical technique. In this study, we tested the hypothesis that topical vancomycin powder applied to the subgaleal space at the time of closure would reduce the incidence of postoperative cranial infections within 30 days of surgery.

Methods

After institutional review board approval, 150 consecutive patients who underwent craniotomy at the Hospital of the University of Pennsylvania between August 2011 and October 2013 were identified retrospectively by Current Procedural Terminology codes for craniotomy (see Table 1). Inclusion and exclusion criteria are summarized in Table 1.

Demographic data known to influence perioperative morbidity were collected. These data included age, body mass index (BMI), diabetes, coronary artery disease (CAD), tobacco use, hypertension, and previous history of craniotomy. Additional data gathered included the use of intravenous steroids, the use of prophylactic antibiotics, operative duration, presence or absence of cranial infection requiring treatment (e.g., antibiotics or reoperation), results of culture for suspected infections, and the timing of the infection. For a subset of patients, serial measurements of vancomycin levels from the wound drain and peripheral blood (n = 5) were available. Wound and serum pH values were also collected postoperatively at serial intervals of 0, 6, and 12 hours. Each patient was followed until the last available follow-up as an outpatient to capture data on any latent infections.

Each patient received the standard of care for craniotomy procedures. The 75 control patients in this series were treated chronologically before the 75 patients treated with vancomycin. This standard included preoperative and postoperative antibiotic prophylaxis with intravenous cefazolin (1–2 g within 30 minutes of incision and 2 repeat postoperative doses spaced 8 hours apart). If a patient had a documented penicillin allergy, 1 g of vancomycin (both before and after surgery) was administered. Skin preparation was completed with chlorhexidine followed by ChloraPrep (CareFusion). Every patient in the study group received 1 g of vancomycin powder sprinkled evenly over the bone flap (in cases of craniotomy) or over the applied artificial dural layer (in cases of craniectomy) (Fig. 1). A Hemovac drain was left in the subgaleal compartment. Each wound was closed with 2-0 Vicryl sutures and staples at the skin, and each incision was dressed with Telfa nonadherent dressing (Covidien) and Tegaderm adhesive (3M). The dressings were removed on postoperative Day 1. Staples were removed between postoperative Days 10 and 14.

Descriptive statistics (means and SDs) were used for all parameters. Fisher exact tests, 2-sample proportion z-tests, and unpaired t-tests were used to assess categorical and continuous variables and their interrelationships. An independent rater, blinded to grouping and patient identification, performed all data collection and analysis in collaboration with a biostatistician (A.S.O. and A.R).

Results

This retrospective review of 150 patients who underwent craniotomy yielded 75 controls and 75 patients who received vancomycin. Groups were matched according to demographic criteria; there were no significant differences in terms of age, BMI, sex, previous surgery, CAD, tobacco use, steroid use, diabetes, or hypertension (Table 1). The vancomycin group was found to have a longer operative duration than the control group (mean 231 ± 107 minutes vs 191 ± 89 minutes, respectively; p < 0.05). In the control group, there were 51 tumor, 6 trauma, 7 vascular, and 9 functional craniotomies. In the vancomycin-treated group, there were 39 tumor, 4 trauma, 7 vascular, and 30 functional craniotomies. No additional group differences were noted.

The primary end point of the study was incidence of SSIs in the vancomycin and matched-control patients. There was a significant difference in SSI rates. A total of 6 patients experienced infection (overall incidence of 4% [6 of 150]): 5 controls and 1 of 75 patients who received vancomycin (p < 0.05). The overall incidence of infection in the control group was 6.7% and in the experimental group was 1.3% (number needed to treat 19; relative risk reduction 81%; OR 0.189 95% CI 0.02–1.67). In all cases of infection, the bacteria were cultured. Details of the infection cases are summarized in Table 2.

Secondary outcome measures included assessments of tissue pH and vancomycin concentrations and time to infection. The mean local vancomycin concentration, measured from the wound drains, was 499 μg/ml. The serum vancomycin concentrations, meanwhile, were undetectable, with a lower limit of detectability of 3.5 μg/ml in our clinical laboratories (Table 3). The mean postoperative-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Patients (n = 75)</th>
<th>Treated Patients (n = 75)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52.1 ± 16.6</td>
<td>49.4 ± 15.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 5.7</td>
<td>28.1 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>38</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Previous op</td>
<td>17</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>CAD</td>
<td>7</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>7</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Previous tobacco use</td>
<td>18</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid use</td>
<td>69</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Length of op (mins)</td>
<td>191 ± 89</td>
<td>231 ± 107</td>
<td>0.01†</td>
</tr>
<tr>
<td>SSI</td>
<td>5</td>
<td>1</td>
<td>0.048†</td>
</tr>
</tbody>
</table>

NS = not significant.
* Patients were included if they were over the age of 18 years, underwent open craniotomy, and had a wound designation of “clean” for their index surgery. Values shown are mean ± SD or number of patients.
† Significant result.

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Surgical site infections comprise a high proportion of hospital-associated infections. The incidence of SSI after craniotomy ranges between 2% and 5%.4,9 The main finding of this study of 150 consecutive cases was a reduction in the incidence of SSIs treating patients vs 15% [11 of 72] in control patients), and a significantly reduced overall infection rate after the use of vancomycin. We also analyzed the time to infection in the patients in our study with a mean follow-up of > 7 months in each group. Each infection in both groups occurred within 10–34 days of the study. These data support the hypothesis that the application of vancomycin powder does not prevent only early surgical site infections.

In a subset of patients, we examined the pH levels and vancomycin concentrations locally and systemically. Serum vancomycin levels were undetectable, whereas the local concentrations of vancomycin were supratherapeutic. Despite maximal medical therapies, SSI continues to plague patients who undergo surgery. Topical vancomycin has been examined as a potential adjunct to standard antibiotic prophylaxis in spinal surgery. The authors of a recent meta-analysis of approximately 6000 patients who underwent spine surgery across 10 studies concluded that local application of vancomycin reduced superficial and deep SSIs.7 It is important to note that topical vancomycin prevents S. aureus infection, the leading cause of SSIs.9 However, the positive effects observed in many of these studies may plateau when baseline infection rates are already exceptionally low. In the setting of baseline infection rates of ≤ 1%, vancomycin does not seem to provide additional benefit.19

In the present study, 1 patient in the treatment group (BMI 57 kg/m²) had a postoperative SSI (methicillin-resistant S. aureus). There were 5 infections in the matched-control group. Our findings are consistent with data from spine surgeries.3 As 2 examples from the posterior cervical fusion literature, Caroom et al.2 documented a substantial reduction in infections (0% [0 of 40] in vancomycin-treated patients vs 15% [11 of 72] in control patients), and Heller et al.3 noted complete elimination of deep infections and a significantly reduced overall infection rate after the use of vancomycin. We also analyzed the time to infection of all the patients in our study with a mean follow-up of > 7 months in each group. Each infection in both groups occurred within 10–34 days of the study. These data support the hypothesis that the application of vancomycin powder does not prevent only early surgical site infections.

In a subset of patients, we examined the pH levels and vancomycin concentrations locally and systemically. Serum vancomycin levels were undetectable, whereas the local concentrations of vancomycin were supratherapeutic. This finding is consistent with the hypothesis that the efficacy of topical vancomycin is realized locally. This hypothesis was tested specifically in pediatric patients. Armaghani et al.1 found that mean vancomycin levels peaked at 2.5 μg/ml, which is below our clinical laboratory limit.

**TABLE 2. Characteristics of patients with postoperative SSI**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Hypertension</th>
<th>BMI (kg/m²)</th>
<th>Craniotomy Type</th>
<th>Revision Op</th>
<th>Vancomycin Powder Used</th>
<th>Pathogen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>28</td>
<td>GBM</td>
<td>N</td>
<td>57</td>
<td>Lt parietooccipital</td>
<td>N</td>
<td>Y</td>
<td>Methicillin-resistant S. aureus†</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>62</td>
<td>Meningioma</td>
<td>Y</td>
<td>33</td>
<td>Lt frontal</td>
<td>N</td>
<td>N</td>
<td>Propionibacterium acne</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>57</td>
<td>Parietal metastasis</td>
<td>N</td>
<td>33</td>
<td>Lt frontoparietal</td>
<td>Y</td>
<td>N</td>
<td>Coagulase-negative S. aureus, P. acne</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>39</td>
<td>GBM</td>
<td>N</td>
<td>26</td>
<td>Lt temporal</td>
<td>Y</td>
<td>N</td>
<td>P. acnes</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>28</td>
<td>Low-grade glioma</td>
<td>N</td>
<td>19</td>
<td>PEEK cranioplasty</td>
<td>Y</td>
<td>N</td>
<td>Stenotrophomonas maltophilia, viridans streptococcus</td>
</tr>
</tbody>
</table>

DHC = decompressive hemicraniectomy; GBM = glioblastoma multiforme; PEEK = polyetheretherketone; TBI = traumatic brain injury.

* None of these patients had diabetes or CAD or used tobacco.
† This organism was vancomycin sensitive.
of detection (3.5 μg/ml) and well below vancomycin toxicity levels (> 15–25 μg/ml). The possibility that topical vancomycin exerts its effect locally is also supported by our measured local concentrations of nearly 500 μg/ml, which are in excess of the mean inhibitory concentration necessary for antimicrobial activity. Finally, we examined tissue pH levels. We found that tissue fluid was slightly alkaline in the hours after surgery, an unexpected finding given that vancomycin powder is prepared as a salt with hydrogen chloride. These findings are in accord with those in the spine literature.

The costs of SSI are high in terms of both morbidity and hospital expense. Deep cranial wound infections may compromise the bone flap, dura, and brain and necessitate additional surgeries and prolonged antibiotic use. In severe cases, SSI may lead to abscess and death. For patients who require chemotherapy and radiotherapy, cranial infections can forestall these adjunctive therapies and hasten their demise. SSIs place substantial financial burdens on patients, families, hospitals, and the nation. Beyond the direct costs of treatment, lost wages and economic productivity compound the financial impact. In the Northeast, health care insurers have begun auditing hospital readmissions to scrutinize the quality of care given during the original admission. Should insurers begin withholding hospital reimbursements related to the treatment of iatrogenic infections, the impact on academic medical centers that treat a disproportionate number of severely ill patients would be dramatic. Finally, hospital readmission rates are quantified as a health care metric and are reported on governmental websites. In turn, quality metrics affect hospital referral and reimbursement patterns.

The strength of the conclusions from the present data set is limited by a number of factors. This investigation was a retrospective study of the senior author’s practice at a single institution. In this respect, this study is no different than a large number of spinal studies that examined vancomycin efficacy. In addition, the possibility of a Hawthorne effect on the presented data is important to consider. Any institutional or departmental initiative to reduce infection rates may lead to a generalizable increase in attention to good practice and sterile technique, which in turn could result in a decrease in infection rates and confound retrospective results. For these reasons, a prospective randomized trial is warranted to determine whether these observations would generalize to a larger cohort of patients undergoing craniotomy, which would eliminate any risk of surgeon bias or a Hawthorne effect. In our study, there were more functional craniotomies in the case group than in the control group. The average operative time in the case group was also longer than that in the control group (231 vs 192 minutes, respectively). Because operative duration is associated with an increased risk of SSI, we might predict a higher rate of infection in the case group. Instead, we found the opposite; consequently, we do not believe that this altered the significance of the findings. We conclude that the vancomycin effect was strong enough to counterbalance any expectation of higher infection associated with longer operative durations.

Conclusions

In this retrospective study of 150 patients who underwent craniotomy, the use of topical vancomycin was associated with a reduced SSI rate. Vancomycin concentrations were supraphysiological in the subgaleal space immediately after surgery but undetectable in the circulating serum. We hypothesize that topical vancomycin use reduces infection rates by directly affecting any local inoculum at the time of surgery. A randomized prospective trial is warranted.

References

9. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pol-

Author Contributions
Conception and design: Abdullah, Richardson, Lucas. Acquisition of data: Abdullah, Attiah. Analysis and interpretation of data: Abdullah, Olsen, Lucas. Statistical analysis: Abdullah, Olsen, Richardson. Study supervision: Lucas. Reviewed submitted version of manuscript: Abdullah. Approved the final version of the manuscript on behalf of all authors: Abdullah. Statistical analysis: Abdullah, Olsen, Richardson. Administrative/technical/material support: Lucas. Study supervision: Lucas.

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