The effect of vancomycin powder on bone healing in a rat spinal rhBMP-2 model

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OBJECTIVE This study aims to quantify the impact of vancomycin powder application on new bone formation and spine fusion rates in a rat posterolateral arthrodesis model.

METHODS Thirty-six female Sprague-Dawley rats underwent a posterolateral lumbar spinal fusion (PLF) at the L-4 and L-5 vertebrae. Fusion was elicited via implantation of an absorbable collagen sponge containing 3 μ g rhBMP-2. Rats were divided into 3 groups: no vancomycin (control), standard-dose vancomycin, and high-dose vancomycin, based on what was applied to the fusion bed. Clinical studies typically describe the application of 1 g vancomycin into the surgical wound. Presuming an average individual patient weight of 70 kg, a weight-based equivalent dose of vancomycin powder was applied subfascially in the PLF model constituting a “standard-dose” treatment group (14.3 mg/kg, n = 12). To determine whether there is a critical threshold beyond which vancomycin increases the risk of pseudarthrosis, a 10-fold higher dose was administered to a “high-dose” treatment group (143 mg/kg, n = 12). No vancomycin powder was applied to the surgical site in the control group (n = 12). Fusion was evaluated with plain radiographs at 4 and 8 weeks after surgery. The spines were harvested after the 8-week radiographs were obtained and evaluated using manual palpation, microCT analysis, and histological analysis.

RESULTS Radiographs demonstrated equivalent bridging bone formation in all groups. No significant differences in fusion scores were seen in the standard-dose (mean 2.25) or high-dose (2.13) treatment groups relative to untreated control animals (1.78). Similarly, fusion rates did not differ significantly different between vancomycin-treated animals (100% for both groups) and control animals (92%). Quantification of new bone formation via microCT imaging revealed no significant between-groups differences in the volume of newly regenerated bone (control vs standard-dose vancomycin, p = 0.57; control vs high-dose vancomycin, p = 0.53).

CONCLUSIONS This is the first in vivo study to specifically address the development of pseudarthrosis after intrawound application of vancomycin during fusion surgery. Our results demonstrate that vancomycin powder does not inhibit fusion rates at a dose that is the weight-percentage equivalent of what is routinely used by surgeons. Moreover, bone formation and fusion rates were not reduced even after administration of a vancomycin dose that is 10-fold higher than that which is typically administered clinically. Our findings suggest that if there is a critical threshold above which vancomycin inhibits bone healing, such a dose is out of the range which might be considered reasonable for clinical use.

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KEY WORDS vancomycin; infection; pseudarthrosis; fusion; MRSA

HISTORICALLY, local application of antibiotics during surgery has been limited to the treatment of periprosthetic joint infections. However, since 2011, a number of clinical studies have demonstrated the efficacy of intrawound vancomycin powder application

in the reduction of postoperative infection rates in spine surgery.^{4,22,25,26,27} This strategy aims to eradicate bacteria through achievement of local supratherapeutic antibiotic levels for a short period of time postoperatively.^{2,27} Its local application avoids the systemic side effects associated

ABBREVIATIONS ACS = absorbable collagen sponge; AP = anteroposterior; H & E = hematoxylin and eosin; MRSA = methicillin-resistant *Staphylococcus aureus*; MT = Masson's trichrome; PLF = posterolateral lumbar spinal fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2; ROI = region of interest.

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with intravenous administration because it is not effectively absorbed from the wound into the circulation. Multiple studies have subsequently confirmed the attractive safety profile of topical vancomycin in children and adults alike.^{2,5,22,26}

Vancomycin powder is often used in the setting of spine fusion, with instrumentation posing an increased risk for postoperative infection. In this context, there remains concern that high local concentrations of vancomycin may have a negative effect on bone healing and ultimately inhibit successful arthrodesis. Clinical studies to date have failed to make a definitive determination regarding the effect of vancomycin on the rate of pseudarthrosis.^{5,15,27} This concern is supported by *in vitro* studies that suggest that vancomycin is toxic to differentiating osteoblasts at high doses.²³ While the ramifications of these findings have not been shown to affect bone formation in a rat femoral defect model,²⁴ as of yet, the effect of vancomycin powder application on the rates of spinal arthrodesis has not been properly evaluated. Such information is critical to the formulation of protocols to prevent surgical-site infections. This study aims to quantify the impact of vancomycin powder application on new bone formation and spinal fusion rates utilizing a rat posterolateral arthrodesis model.

Methods

Study Design

This study was conducted in accordance with the protocol approved by the Institutional Animal Care and Use Committee at Northwestern University and with Animal Welfare Assurance with the Office of Laboratory Animal Welfare (A3283-01). We found that in the experimental treatment groups, 80% power can be obtained with 12 animals per group and an effect size of 3. A total of 36 female Sprague-Dawley rats were divided into 3 treatment groups: no vancomycin (positive control), standard-dose vancomycin, and high-dose vancomycin. An equivalent dose of vancomycin powder for the rat was calculated based on clinical studies that use 1g vancomycin powder for an average individual with a weight of 70 kg. The “standard-dose” group (14.3 mg/kg; *n* = 12) was treated with a dose of vancomycin based on this usage. Furthermore, in an attempt to determine whether there is a critical threshold beyond which vancomycin increases the risk of spinal pseudarthrosis, a dose 10-fold higher than that received by the standard-dose group was administered to a “high-dose” treatment group (10 g weight percentage equivalent; 143 mg/kg; *n* = 12). No vancomycin powder was applied to the surgical site in the control group (*n* = 12).

All rats underwent a posterolateral lumbar spinal fusion (PLF) at the L-4 and L-5 transverse processes using an absorbable collagen sponge (ACS) containing 3 µg recombinant human bone morphogenetic protein-2 (rhBMP-2). A dose range of 3–10 µg rhBMP-2/ACS is classically used as a positive control in this model, eliciting fusion at a rate of 100%;²⁰ in this study, we chose the low end of this range to increase the chance of detecting any inhibitory effect of vancomycin on spine fusion rates. Of note, a negative control group was not used, as ACS alone has previously demonstrated a 0% fusion rate and

thus serves as a historical control.^{12,18} Radiographic fusion was evaluated 4 and 8 weeks postoperatively. Spines were harvested at 8 weeks and subsequently evaluated using manual palpation fusion scoring, microCT, and histological analysis. It should be noted that the use of locally applied vancomycin powder and rhBMP-2 in posterolateral fusions is not FDA approved.

Surgical Technique

Rats were administered continuous inhalational isoflurane at a dose of 2%–3% in 100% oxygen via an anesthesia delivery system. Utilizing our previously described surgical technique,^{12,13,18} a posterior midline incision was made over the lumbar spine, followed by 2 separate fascial incisions 4 mm from the midline. The transverse processes of L-4 and L-5 were exposed using a muscle-splitting approach via blunt dissection down to the periosteum. The surgical site was irrigated with gentamicin, and the L4–5 fusion bed was prepared. A high-speed bur was used to decorticate the exposed transverse processes. The ACS, containing 3.0 µg rhBMP-2, was then implanted bilaterally in the paraspinal musculature between the transverse processes. Animals from the vancomycin treatment groups received vancomycin powder application, which was evenly distributed into the surgical site bilaterally, overlying the fusion bed subfascially. The epiaxial musculature overlying the vertebral spinous processes was opposed, and fascial incisions were closed using a 3-0 Monocryl absorbable suture (Ethicon, Inc.) in a simple interrupted fashion. Skin incisions were closed using wound clips; 5 ml of warm lactated Ringer solution were then administered intraperitoneally. Rat cages were maintained on a heating pad, and animals were monitored every 15 minutes for the 1st hour after surgery. Buprenorphine hydrochloride and meloxicam were administered for 1–3 days as needed for pain control. Standard rat chow and water were provided for *ad libitum* consumption.

Determination of Fusion

Plain anteroposterior (AP) radiographs were obtained with an APR-VET Console (Sedecal USA, Inc.) at 4 and 8 weeks after surgery. After the 8-week radiographs were obtained, the animals were humanely killed, and their lumbar spines were harvested for further evaluation. All harvested spines were manually palpated for evidence of successful fusion by 3 independent, blinded observers using a previously published scoring system, whereby 0 indicates no bridging bone, 1 indicates unilateral bridging, 2 indicates bilateral bridging, and 3 indicates bilateral bridging with abundant bone formation.^{12,18} Individual scores for each specimen were then averaged. As with the human patient population, in which unilateral bridging constitutes successful fusion, spines with an average score ≥ 1.0 were considered successfully fused.

Quantitative MicroCT Imaging

Harvested specimens were imaged using a MicroCT-40 scanner (Scanco, Inc.). In a modification of a previously published protocol, 2 spines were placed in a plastic holder with the spines' axes parallel to the scanner's ro-

tation axis.^{12,13,18} The pair of spines was scanned simultaneously using an x-ray voltage tube of 70 kVp and 114 μ A, and the integration time for each projection was 0.200 seconds. Reconstruction was performed with 37-mm isotropic volume elements (voxels), and the 540-contiguous slice data sets encompassed the L-4 and L-5 transverse processes. Using the Scanco software suite, the amount of newly formed bone between the L-4 and L-5 transverse processes was quantified for each specimen. Regions of interest (ROIs) were manually defined in each slice and included the 2 fusion beds of each spine. Within the ROI, voxels more absorbing than a predefined threshold were identified as bone and summed by the Scanco software to give the total bone volume. The threshold was selected by examining several specimens and selecting the value best reproducing the structure of newly formed bone, as seen in the gray-scale reconstructions. As calculated from the Scanco bone mineral density phantom, the selected threshold of 450 mg/cm³ corresponded to hydroxyapatite (hAp). The host bone volume in the L-4 and L-5 transverse processes was quantified in 4 control animals outside of the study groups and averaged (267 ± 32 mm³). The volume of new bone formed was calculated by subtracting the mean host bone volume from total bone volume measured in each animal.

Histological Analysis

Representative spines from each group were subjected to histological analysis, which was performed at the Northwestern University Mouse Histology Phenotyping Laboratory. After detachment of surrounding soft tissue, spine specimens were fixed in 10% neutral-buffered formalin, decalcified in HCl/EDTA, and embedded in paraffin. Serial sagittal cuts were made at 4-mm intervals along the L4–5 transverse processes. Sections were subsequently stained with hematoxylin and eosin (H & E) and Masson's trichrome (MT).

Statistical Methods

Fusion scores and quantification of new bone volume (mean values derived from microCT analysis) were evalu-

ated using a 2-tailed Student t-test for normally distributed data. A Fisher exact test was used to compare fusion rates between groups. A p value < 0.05 was considered statistically significant.

Results

Qualitative radiographs demonstrated reproducible bridging bone formation in all groups (Fig. 1). Only 1 animal showed no radiographic evidence of bridging bone, and this animal was in the control group. Eight weeks after surgery, blinded manual palpation of the harvested spines demonstrated no significant difference in fusion scores in either the standard- or high-dose vancomycin groups (2.25 ± 0.47 and 2.13 ± 0.55 , respectively) relative to the control animals (1.78 ± 0.79 , Fig. 2 left). Similarly, fusion rates did not differ significantly between the vancomycin-treated groups (100% for both groups) and the control animals (92%, Fig. 2 right), demonstrating that vancomycin powder application does not inhibit spine fusion in the rat PLF model.

Quantification of newly regenerated bone via microCT imaging established mean new bone volumes at 1752.3 mm³ (± 929 mm³), 1404.9 mm³ (± 675 mm³), and 2156.5 mm³ (± 764 mm³) in the untreated, standard-dose vancomycin, and high-dose vancomycin groups, respectively (Fig. 3 left), which were not significantly different from one another (control vs standard-dose vancomycin, $p = 0.57$; control vs high-dose vancomycin, $p = 0.53$). Representative 3D renderings of microCT images are shown for fused spines in each group (Fig. 3 right).

Histological analysis confirmed solid fusion masses between the transverse processes of L-4 and L-5 in spine specimens from all 3 groups (Fig. 4). The H & E-stained sections demonstrate cancellous bone formation traversing the transverse processes of L-4 and L-5 vertebrae and bony trabeculae (dark, solid pink) surrounding marrow spaces. Osteoid deposition is seen within the marrow spaces, marked by a shift in matrix color (darker purple represents areas of mineralization). The outer fibrous layer of periosteum, composed of collagen and fibroblasts, marks the extent of bony fusion mass, to which skeletal

FIG. 1. Representative AP radiographs of rat spines obtained 8 weeks after surgery depicting bridging bone formation between the L-4 and L-5 transverse processes in the 3 treatment groups. White arrows indicate bridging bone.

FIG. 2. **Left:** Fusion scores from blind manual palpation analysis at 8 weeks after surgery. **Right:** Fusion rates of each treatment based on manual palpation scores. No significant difference was found between the standard-dose, high-dose vancomycin, and control groups with respect to fusion scores.

muscle fibers of the paraspinal musculature (light pink) attach. These muscle fibers appear dark red on MT-stained sections. Connective tissue and collagen appear blue under MT staining and can be identified along the border of the bony fusion mass.

Discussion

Despite the use of systemic antibiotic therapy and sterile technique, surgical-site infections are still a major concern for surgeons and can have a devastating effect on outcomes. More than 60% of clinical isolates from wound infections in the US, including methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *S. aureus*, are resistant to cephalosporins.^{16,17} Numerous studies have shown that vancomycin powder significantly reduces the incidence of postoperative infection.^{5,15} Powder application of vancomycin is an attractive adjunct to systemic intravenous administration because it provides a means of achieving a very high local bactericidal level, with local concentrations up to 1000-fold higher than the mean inhibitory concentration for MRSA and coagulase-negative *S. aureus*.⁷ Applying vancomycin topically avoids potential systemic side effects, but the literature regarding its impact on bone healing and fusion rates is inconclusive.

In our rat PLF model, plain radiographs, manual palpation, microCT imaging, and histological analysis all found no significant difference in fusion scores or rates between untreated control animals and our standard-dose (weight percentage equivalent) vancomycin groups. A high-dose group was included to test the potential effects of excessive local antibiotic concentrations. Similarly, there were no differences in fusion scores or rates relative to controls. Based on these data, if there exists a critical threshold above which vancomycin inhibits bone healing, such a dose is higher than the range that might be considered reasonable for clinical use. While these results are promising, it is pertinent to keep in mind that we used rhBMP-2/ACS to elicit fusion (as it provides the most reliable positive control) while administering a dose that was unlikely to oversaturate the fusion response (3 μ g rhBMP-2 per animal; 1.5 μ g/side). It is certainly a valid argument to consider that an inhibitory effect may be observed at a lower dose of rhBMP-2, but performing a dose-response analysis was outside the scope of this study.

To date, clinical studies that address the risk of pseudarthrosis after vancomycin powder application are limited. In one of the largest studies, Sweet et al. evaluated 1732 patients who underwent thoracic and lumbar instrumented fusions, three of which were identified with pseud-

FIG. 3. **Left:** Fused specimens were analyzed by microCT to compare fusion mass volume (mm^3). Error bars indicate standard deviations. There was no statistically significant difference between the vancomycin-treated groups and the no-vancomycin controls (control vs standard dose vancomycin, $p = 0.57$; control vs high dose vancomycin, $p = 0.53$). **Right:** Representative spine reconstructions from mReprCT are shown for the successfully fused specimens.

FIG. 4. Histological sections of representative fusion masses for control (0 mg vancomycin), standard-dose (14.3 mg vancomycin), and high-dose (143 mg vancomycin) treatment groups. All animals received 3 μ g rhBMP-2/ACS. H & E and MT, original magnification $\times 100$. Figure is available in color online only.

arthrosis in the vancomycin group compared with four in the control group, a difference which was not statistically significant.⁷ In a study of lumbar fusions, Strom et al. also concluded that vancomycin powder was not associated with an increased risk of pseudarthrosis (occurring in 0 of 97 untreated patients vs 1 of 156 treated patients).²⁶ Although these rates are encouraging, the studies were performed retrospectively and not designed to critically compare fusion success. Well-designed prospective trials are needed to provide a meaningful analysis regarding the true pseudarthrosis risk.

Despite a multitude of benefits, there is some evidence to suggest that local vancomycin application may be detrimental to bone healing. Previous animal studies have shown that direct intrawound application of antibiotic powders, including aminoglycosides, quinolones, and gentamicin, can have cytotoxic effects and inhibit osteoblast function.^{11,14,19,23} In vitro studies have shown that vancomycin is less toxic to osteoblasts relative to many other antibiotics.^{1,8,23} Similarly, at a dose of 5 mg/ml, vancomycin was moderately to severely cytotoxic, and also moderately inhibited ALP activity.²³

Although in vitro studies suggest that vancomycin is toxic to differentiating osteoblasts, our study demonstrates that its application in powder form does *not* inhibit fusion rates at a wt% dose equivalent to what is routinely used by surgeons for fusion procedures. One explanation for this contradiction is that when vancomycin is applied locally, systemic absorption of the antibiotic is poor, as shown in the series by Sweet et al.,²⁷ where serum vancomycin levels were nearly undetectable. This may help avoid potentially deleterious systemic effects, such as hypotension, renal toxicity, and the development of resistant organisms.^{9,21,27} Our finding that vancomycin powder has no adverse effect on bone formation in vivo indicates that its dissipation after local application may be rapid enough

to avoid a negative impact on osteoblast precursors. This is supported clinically in the study by Sweet et al.,²⁷ in which drain measurements showed that local vancomycin levels decreased rapidly from 1457 mcg/ml on postoperative Day 0 to 128 mcg/ml on postoperative Day 3. Similar results were observed in a pediatric study, where drain levels measured 403 mcg/ml on postoperative Day 0 and dissipated to 115 mcg/ml on postoperative Day 2. These values are far beyond the minimum inhibitory concentration of 2 mcg/ml for MRSA and MSSA.²

Limitations to the present study are inherent in the utilization of a rodent model. In addition to the anatomical differences between rat and human spines, bone healing in rats typically occurs at a faster rate and may be less susceptible to inhibitory factors. Consequently, because of the different healing patterns, vancomycin powder could have a different effect in humans. Physicians should be cognizant of the fact that the findings of this study may not have a direct correlate in the clinical scenario. It should also be noted that the aforementioned results are specific to rhBMP-2-induced healing and may not be universally applicable to spinal fusion procedures that do not use this growth factor.

Although an autograft-based positive control would have made our findings widely applicable, autograft does not reliably heal in the rat model.¹⁰ Future studies are needed to determine the impact of vancomycin on spine fusion in the setting of bone graft substitutes. Despite this caveat, this model still holds value, as rhBMP-2 has been shown in clinical studies to produce superior fusion rates in single-level lumbar fusions compared with iliac crest autograft,^{6,7} even without the use of instrumentation.³ Lastly, although we did not expect a testable difference, the biomechanical strength of the fusion mass was not evaluated in this study.

Conclusions

Vancomycin powder application does not inhibit fusion rates at a weight percentage dose equivalent to what is routinely used by surgeons in fusion procedures. Bone formation and fusion rates were not reduced even after administration of vancomycin at a dose 10-fold higher than which is typically administered clinically. If there is a critical threshold above which vancomycin inhibits bone healing, such a dose is out of the range that might be considered reasonable for clinical use.

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Disclosures

Erin Hsu reports a consultant relationship with AONA, Bacterin, Bioventus, CeramTec, Globus, Graftys, Lifenet, Medtronic, Pioneer Surgical, Relievant, Stryker Spine, and Synthes. Wellington Hsu reports a consultant relationship with Medtronic, Stryker,

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Supplemental Information

Previous Presentations

Portions of this work were presented in abstract form at the Lumbar Spine Research Society Annual Meeting, Chicago, Illinois, April 9, 2015, as well as in poster form at the Orthopaedic Research Society Annual Meeting, Las Vegas, Nevada, March 28–31, 2015.

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