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Intrawound Vancomycin Decreases the Risk of Surgical Site Infection After Posterior Spine Surgery: A Multicenter Analysis

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Study Design. Secondary analysis of data from a prospective multicenter observational study.

Objective. The aim of this study was to evaluate the occurrence of surgical site infection (SSI) in patients with and without intrawound vancomycin application controlling for confounding factors associated with higher SSI after elective spine surgery.

Summary of Background Data. SSI is a morbid and expensive complication associated with spine surgery. The application of intrawound vancomycin is rapidly emerging as a solution to reduce SSI following spine surgery. The impact of intrawound vancomycin has not been systematically studied in a well-designed multicenter study.

Methods. Patients undergoing elective spine surgery over a period of 4 years at seven spine surgery centers across the United States were included in the study. Patients were dichotomized on the basis of whether intrawound vancomycin was applied. Outcomes were occurrence of SSI within postoperative 30 days and SSI that required return to the operating room (OR). Multivariable random-effect log-binomial regression analyses were conducted to determine the relative risk of having an SSI and an SSI with return to OR.

Results. A total of 2056 patients were included in the analysis. Intrawound vancomycin was utilized in 47% (n = 966) of patients. The prevalence of SSI was higher in patients with no vancomycin use (5.1%) than those with use of intrawound vancomycin (2.2%). The risk of SSI was higher in patients in whom intrawound vancomycin was not used (relative risk (RR) -2.5, $P < 0.001$), increased number of levels exposed (RR -1.1, $P = 0.01$), and those admitted postoperatively to intensive care unit (ICU) (RR -2.1, $P = 0.005$). Patients in whom intrawound vancomycin was not used (RR -5.9, $P < 0.001$), increased number of levels were exposed (RR-1.1, $P = 0.001$), and postoperative ICU admission (RR -3.3, $P < 0.001$) were significant risk factors for SSI requiring a return to the OR.

Conclusion. The intrawound application of vancomycin after posterior approach spine surgery was associated with a reduced risk of SSI and return to OR associated with SSI.

Key words: multicenter, return to OR, SSI, surgical site infection, vancomycin.

Level of Evidence: 2

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There are an estimated 500,000 surgical site infections (SSIs) annually in the United States (U.S.) accounting for up to $1.8 billion additional health care costs annually.[1,2] SSI is associated with an increased length of hospital stay by a median of 2 weeks, higher readmission,

repeat operations, and a two-fold increase in mortality.[2–4] The rate of spine-related SSI ranges between 2% and 13%, depending upon the procedure and pathology being treated.[4–12] SSI has a profound impact on patients' life and health care utilization. Patients may require extended rehabilitation, prolonged antibiotic therapy, multiple surgical procedures for wound debridement and implant revision, revision for pseudoarthrosis, and instrumentation failure, with conservative cumulative costs of $100,000 per patient.[4,8,12]

SSI is being viewed as a "never event" and key metric by which a provider and facility are judged as to the quality of care provided. Reducing the SSI rates is vital for demonstrating safety and containment of health care resource utilization. To mitigate the risk of infection, various techniques have been utilized, including preliminary surgical site preparation with alcohol foam, appropriate timing of intravenous (IV) antibiotics, identification and prophylactic measures for Methicillin resistant Staphylococcus Aureus (MRSA) carriers, utilization of providine or bacitracin in the irrigant, and timely drain removal [3,13–16] One additional technique is the use of local intrawound antibiotic placed at the time of wound closure. The rationale of using local antibiotic is to achieve a local high antibiotic concentration, high bacterial killing rates, and to minimize the systemic toxicity. Buchholz and Engelbrecht[17] first described the use of local antibiotics in 1970; since then, the local application of antibiotic has been investigated in orthopedics, cardiothoracic, vascular, and spine surgeries.[9,18–21] The most common organisms associated with SSI are gram-positive *Staphylococcus aureus* and *Staphylococcus epidermidis*.[22] Therefore, the application of intrawound vancomycin is rapidly emerging as a solution to reduce the SSI following spine surgery specifically associated with these bacteria.

There is insufficient and contradicting evidence on use of vancomycin and its effectiveness at mitigating infection. Several studies have demonstrated that application of local intrawound vancomycin powder significantly reduces infection rates.[4,11,23–30] The addition of prophylactic intrawound vancomycin to standard systemic prophylaxis in elective spine surgery was shown to reduce infection rates from 2.6% to 0.2%.[29] In contrast, others have reported no impact of using intrawound vancomycin on SSI.[12,31] The aim of this multicenter study was to evaluate the risk of SSI in patients with and without intrawound vancomycin application and determine the factors associated with higher SSI after elective spine surgery. The hypothesis of the present study was that intrawound vancomycin decreases the risk of SSI. Outcomes were occurrence of SSI within postoperative 30 days and occurrence of SSI that requires return to the operating room (OR).

MATERIALS AND METHODS

A secondary analysis, of data from a prospective multicenter observational study, was conducted after obtaining approval from the institutional review board of the participating centers. Patients undergoing spine surgery *via* a posterior approach for degenerative spine pathology, between November 2010 and July 2014, at seven academic medical centers sites across the U.S. were included in the study. These sites consisted of both community and academic medical centers. Patients from all sites were dichotomized on the basis of whether intrawound vancomycin was applied. The application of intrawound vancomycin was up to the treating physician. The treatment group was defined as patient receiving local vancomycin powder spread throughout the surgical wound in addition to standard IV systemic prophylaxis. Patients with any of the following associated conditions were not eligible to receive intrawound vancomycin: (1) known allergy to vancomycin, (2) previous spine surgery at the operated level within 6 months, (3) pregnancy, (4) history of Stevens-Johnson syndrome, (5) history of infection at the surgical site, or (6) radiation treatment at the operated level. The control group received standard systemic prophylaxis only.

Patients underwent a posterior spinal surgery with and without fusion for degenerative pathologies, spinal trauma, or tumor. All patients had identical preoperative surgical site preparation specific to each site. Patients received standard antibiotic prophylaxis consisting of 1 g of IV cefazolin within 1 hour of surgical incision followed by 1 g of IV cefazolin every 8 hours for one day postoperative. In patients allergic to penicillin, 900 mg of IV clindamycin was used. Subfascial drains were used and connected to suction canisters. Dressings and drains were kept in place until daily drain output was less than 80 mL per 24 hours. The drains were not clamped, as on the basis of our experience and previously published studies,[29,32] the supratherapeutic levels of local vancomycin are achieved for 2 days without clamping, which is considered enough time to allow for epithelialization to occur. On the basis of the surgeon's preference, the vancomycin group received an additional 1 gram vancomycin powder (Hospira Inc., Lake Forest, IL) for every 10 cm of longitudinal wound length spread throughout the surgical wound upon closure. The powder was placed directly on the muscle, fascia, and subcutaneous tissues taking care not to expose bone graft or dura mater.

Patient demographics were collected, including age, sex, race, height and weight, smoking status, and presence of diabetes, chronic steroid use, and chronic renal insufficiency. Furthermore, the diagnosis, spinal level operated upon, revision *versus* primary surgery, use of instrumentation, arthrodesis, need for postoperative admission to intensive care unit (ICU), number of spinal levels exposed, and length of hospital stay were obtained from the medical record. The presence of SSI was determined by visual wound inspection and contrast-enhanced MRI, which was used in all cases when superficial or deep SSI was suspected. Superficial infections were treated with a spectrum of oral antibiotics directed at the most common offending organisms. Deep infections, in which cultures were obtained, underwent treatment with IV antibiotics on the basis of culture sensitivities and under the direction of an infectious disease consultant. A deep SSI was treated with excision and

debridement of the wound with removal and or exchange of the hardware as deemed necessary. The attending surgeon at each center recorded the incidence of superficial or deep SSI as well as whether the SSI required a return to the OR.

Statistical Analysis

Descriptive statistics examined the mean, standard deviation (SD), and frequency of all demographic and clinical characteristics of the study population as well as the distribution of SSI by site and use of vancomycin. Student *t* tests and Chi-square or Fisher exact tests examined differences in patient characteristics by vancomycin group. Outcomes of SSI and SSI requiring a return to the OR were compared across treatment groups using Chi-square tests. Multivariable random-effect log-binomial regression analyses were conducted to determine the relative risk of having an SSI and an SSI with return to OR. Covariates that were significant at $P < 0.05$ in bivariate log-binomial regression analyses were entered into the multivariable model. Site was included as a random effect *a priori* to account for clustering of patients within site. Analyses were performed using stata statistical software (Version 11.0; Stata Corp, College Station, TX). The stata GLLAMM macro produced estimates of the variance of the random effects for site. The fraction of the variance attributable to differences between sites was calculated by dividing the variance of the site random effect by the total variance in the model (site and participants). The variance for participants was considered to be $\pi^2/3$ for calculation purposes. The stability of the final model was test by adding back in each excluded variable one at a time. Missing data were less than 5% and handled using regression models that imputed the missing values as a function of the other covariates. A P value <0.05 was considered statistically significant.

RESULTS

Patient Demographic and Clinical Characteristics

A total of 2056 patients underwent elective spine surgery for degenerative spine pathologies across seven sites and were included in the analysis. The mean number of levels exposed was 3.6 ± 2.8, 82% (n = 1695) underwent fusion, and 79% (n = 1628) of patients underwent instrumentation. Intrawound vancomycin was utilized in 47% (n = 966) of patients.

The mean length of hospital stay was 5.0 ± 4.7 and 21.1% (n = 434) of patients were admitted to the ICU after surgery. The vancomycin group had significantly higher number of patients with diabetes (21.5% *vs.* 17.7%, $P = 0.03$), steroid use (6.7% *vs.* 4.5%, $P = 0.03$), and fusion rates (84.5% *vs.* 80.6%, p = 0.02) than the no vancomycin group. Patients with chronic renal failure (4.4% *vs.* 3.4%, $P = 0.22$) and obese (37.2% *vs.* 33.9%, $P = 0.26$), were higher in vancomycin group, but this did not reach statistical significance. Table 1 summarizes the patient characteristics in the vancomycin and no vancomycin groups.

SSI by Site and Use of Vancomycin

The site-to-site variation in occurrence of SSI ranged from 1.4% to 5.8% (Table 2). The prevalence of SSI across all sites was 3.8% (n = 77) (Table 3). A significantly higher rate of SSI was found in patients with no vancomycin use (5.1%, n = 56) than those with use of intrawound vancomycin (2.2%, n = 21) ($P < 0.001$). There was a significantly higher rate of SSI requiring return to OR in the no vancomycin group (3.9%, n = 42) than those with use of intrawound vancomycin (0.7%, n = 7) ($P < 0.001$).

Log-Binomial Regression Analyses

Multivariable random-effect log-binomial regression analysis found that no vancomycin use was a statistically significant risk factor for SSI [relative risk (RR) -2.5, confidence interval (CI) -1.5 to 4.1, $P < 0.001$] and SSI requiring return to the OR (RR -5.9, CI 2.6–13.2, $P < 0.001$) (Table 4). Additional risk factors for SSI were increased number of levels exposed (RR -1.1, CI 1.0–1.2, $P = 0.01$) and postoperative ICU stay (RR -2.1, CI -1.3 to 3.6, $P = 0.005$). Increased number of levels exposed (RR -1.1, CI -1.0 to 1.2, $P = 0.001$) and postoperative ICU stay (RR -3.3, CI -1.8 to 6.2, $P < 0.001$) were also significantly associated with SSI that required a return to the OR. Site contributed significantly to the model and accounted for 3% of the variance in SSI and 20% of the variance in SSI that required return to the OR.

DISCUSSION

In this analysis, utilizing multicenter observational data on contemporaneous patients, we demonstrated that the intrawound application of vancomycin after posterior spine surgery is associated with reduced overall SSI and SSI requiring a return to the OR. Multivariable analyses also found that increasing the number of operated levels and postoperative ICU stay were independent risk factors for SSI.

Previous studies have reported conflicting results on impact of intrawound vancomycin application on SSI rates.[5,9,33] Analogous to our findings, several retrospective, single-center, observational studies have advocated the use of intrawound vancomycin to prevent SSI.[4,7,11,23,25–27,29,30,34] In our analysis, across all the sites included in the study, the risk of SSI (5.1% *vs.* 2.2%) and SSI requiring return to OR (3.9% *vs.* 0.7%) was higher in patients who did not have application of intrawound vancomycin. A meta-analysis performed by Khan *et al*[9] reported 2.99 times higher likelihood of SSI when intrawound vancomycin power was not used in spine surgery. The protective benefit of intrawound vancomycin is demonstrated in both instrumented and noninstrumented spine surgeries.[23] In contrast, a study by Tubaki *et al*[12] demonstrated that intrawound vancomycin had a minimal impact on reducing SSI. On the basis of their prospective randomized control trial of 907 patients, they reported no significant difference (1.61% *vs.* 1.68%) in the rates of SSI among the patients in treatment group (intrawound vancomycin) and control group (no

TABLE 1. Demographic and Clinical Characteristics of Study Participants (N = 2056)

Characteristic	Total	Vancomycin (N = 966)	No Vancomycin (N = 1090)	*P*
Demographic Characteristics				
Age in years, Mean ± SD	58.8 ± 14.8	60.5 ± 13.6	59.5 ± 13.9	0.09
Sex, N (%)				
Female	1042 (50.7)	489 (50.6)	553 (50.7)	0.96
Male	1014 (49.3)	477 (49.4)	537 (49.3)	
Race, N (%)				
White	1801 (87.3)	850 (88.0)	951 (87.3)	0.61
Nonwhite	255 (12.7)	116 (12.0)	139 (12.7)	
BMI category, N (%)				
Normal	504 (24.5)	236 (24.4)	268 (24.6)	0.26
Overweight	9823 (40.0)	371 (38.4)	452 (41.5)	
Obese	729 (35.5)	359 (37.2)	370 (33.9)	
Current smoker, N (%)	504 (24.5)	228 (23.6)	276 (25.3)	0.37
Diabetes, N (%)	401 (19.5)	208 (21.5)	193 (17.7)	0.03
Steroid use, N (%)	114 (5.5)	65 (6.7)	49 (4.5)	0.03
Chronic renal insufficiency	80 (3.9)	43 (4.4)	37 (3.4)	0.22
Clinical characteristics				
Location, N (%)				
Lumbar-sacral	1409 (68.5)	685 (70.9)	724 (6.4)	<.001
Cervical	525 (25.5)	212 (22.0)	312 (28.7)	
Thoracic	122 (5.9)	69 (7.1)	53 (4.9)	
Revision surgery, N (%)	642 (31.2)	314 (32.5)	328 (30.1)	0.24
Instrumentation, N (%)	1628 (79.2)	755 (78.2)	873 (80.1)	0.28
Arthrodesis, N (%)	1695 (82.4)	816 (84.5)	879 (80.6)	0.02
ICU stay, N (%)	434 (21.1)	206 (21.3)	228 (20.9)	0.82
Number of spine levels exposed	3.6 (2.8)	3.6 (2.9)	3.6 (2.7)	0.67
Length of stay in days, Mean ± SD	5.0 ± 4.7	5.2 ± 4.4	4.9 ± 4.9	0.17

BMI indicates body mass index; ICU, intensive care unit.

vancomycin). There are several flaws in the study by Tubaki *et al*,[12] no *a priori* sample size calculation was performed and the rate of SSI was too low (n = 8, 1.68% in each group), making it difficult to derive any statistical significance. Furthermore, the authors did not evaluate confounding risk factors known to increase the risk of SSI. In addition Martin *et al*,[31] in their retrospective single-center study of 306 patients, reported that the use of intrawound vancomycin was not protective for deep SSI in patients undergoing thoracolumbar fusion for spinal deformity. In our analysis, the rate of SSIs was significantly lower in the intrawound vancomycin cohort, despite having a higher number of patients with known risk factors for SSI, such as diabetes and older age. Furthermore, there were a higher number of patients with obesity, chronic renal failure, and postoperative ICU stay in the vancomycin cohort than the control group, but this did not reach statistical significance.

Intrawound vancomycin powder is an appealing intervention, given minimal to no local or systemic adverse events attributable to intrawound vancomycin application.

TABLE 2. Distribution of SSI by Site and Use of Vancomycin (N = 2056)

Site	Total SSI N (%)	Vancomycin N (%)	No Vancomycin N (%)
A	5 (2.4%)	2 (2.3%)	3 (2.4%)
B	14 (4.3%)	4 (2.5%)	10 (6.1%)
C	16 (3.9%)	6 (3.1%)	10 (4.7%)
D	19 (5.0%)	1 (.5%)	18 (11.1%)
E	14 (5.8%)	4 (4.0%)	10 (7.1%)
F	5 (1.4%)	3 (1.7%)	2 (1.2%)
G	4 (2.7%)	1 (2.8%)	3 (2.7%)

SSI indicates surgical site infection.

TABLE 3. Prevalence of SSI by Use of Vancomycin (N = 2056)

Characteristic N (%)	Total	Vancomycin (N = 966)	No Vancomycin (N = 1090)	*P*
Total SSI	77 (3.8%)	21 (2.2%)	56 (5.1%)	<0.001
SSI that required return to OR	49 (2.4 %)	7 (0.7%)	42 (3.9%)	<0.001
SSI that did not require return to OR	28 (1.4 %)	14 (1.5%)	14 (1.3%)	0.75

OR indicates operating room; SSI, surgical site infection.

Reported or potential side effects include tissue irritation resulting in neuritis or seroma formation, development of vancomycin-resistant organisms, selection of gram-negative organisms, inhibition of osteoblasts with resultant pseudoarthrosis, renal toxicity, and anaphylactic reaction. Ghobrial *et al*[35] reported a 1.4% (n = 14) rate of postoperative sterile seroma in patients who had intrawound vancomycin. The authors postulated that fat necrosis or an occult infection at undetectable levels due to a high local vancomycin concentration might attribute to the seroma occurrence. The local concentration of vancomycin, based on levels obtained from surgical drains, has been shown to range between 263 and 2938 μg/mL on the day of surgery with a trend down to undetectable levels by postoperative day 4.[29] This creates a concentration that is nearly a thousand fold higher than the minimum inhibitory concentration for MRSA and coagulase-negative staphylococcus making the development of resistant organisms low.[29,32] Intrawound application of vancomycin powder may, however, select out gram-negative spine infections.[25] Therefore, to further reduce the risk of SSI, one may consider adding another antibiotic with gram-negative or broad polymicorbial coverage, which can achieve minimal systemic absorption, high local concentration, and minimal local adverse events.

The impact of intrawound vancomycin on osteogenesis and fusion rates following spine surgery is not well reported. *In vitro* studies have demonstrated that a high local concentration up to 10,000 μg/mL or 3 to 6 mg/cm^2 is needed to inhibit osteogenesis.[5,36,37] As demonstrated by drain concentrations, the doses are well below these concentrations. However, no well-done clinical studies have evaluated the effect of intrawound vancomycin on pseudoarthrosis rates.[38] Systemic renal toxicity is unlikely due to the low serum levels noted in multiple studies.[29,32] Anaphylactic reaction is a possibility and was reported by Mariappan *et al*[39] describing a case of circulatory collapse about 30 minutes after application of 1 gram of vancomycin over the dura and exposed vertebrae. The currently used dose of 1 to 2 g is empirical; therefore, further pharmacokinetic studies are needed to determine effective and safe dose for spine surgery.[36] For this study, we utilized 1 g per 10 cm of longitudinal incision length. With the current empiric dose regimen, a single local application of vancomycin costs between $12 and $40. This makes it an extremely cost-effective intervention given a SSI requires on average $3000 to $25,446 more for their care.[2,40] Previous studies reported cost savings of using intrawound vancomycin in spine surgery ranging from $220,000 to $500,000 per 100 patients.[5,7,30]

Several limitations need to be considered when interpreting results. The differences in pre and peri-operative measures to prevent infection at each site were not analyzed in this study, which might have confounded the overall SSI rates. Given the multicenter nature of this study and the diverse patient population undergoing posterior spine surgery, the rate of SSI can be somewhat generalized. We analyzed the prevalence of SSI and return to OR rates at

TABLE 4. Multivariable Random-Effect Log-binomial Regression Model of SSI and SSI with Return to OR (N = 2056)

	Total SSI		SSI OR	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Vancomycin: No *vs*. yes (ref)	2.5 (1.5, 4.1)	<0.001	5.9 (2.6, 13.2)	<0.001
Overweight BMI *vs*. normal	0.99 (0.5, 1.8)	0.97	0.97 (0.47, 2.0)	0.95
Obese BMI *vs*. normal	1.7 (0.9, 3.0)	0.08	1.2 (0.56, 2.6)	0.64
Number of levels exposed	1.1 (1.01, 1.2)	0.01	1.1 (1.0, 1.2)	0.001
ICU stay: yes *vs*. no (ref)	2.1 (1.3, 3.6)	0.005	3.3 (1.8, 6.2)	<0.001
Diabetes: yes *vs*. no (ref)	0.64 (0.34, 1.2)	0.17	0.81 (0.37, 1.8)	0.60
Site variance	0.10 (0.09)	0.82 (0.37)		

Model included a random effect to account for clustering of patients within site. BMI indicates body mass index; CI, confidence interval; ICU, intensive care unit; OR, operating room; ref, reference; RR, relative risk; SSI, surgical site infection.

30 days after the index spine surgery. The impact of intrawound vancomycin on 90-day or 1-year SSI was not analyzed. The rate of SSI is high within 30 days postoperatively and decreases subsequently; therefore, this time point was chosen *a priori*. However, due to lack of high-level evidence on local and systemic adverse effects, it is unclear whether the intrawound vancomycin should be a standard of care or to be used only for high-risk patients. Finally, there are limitations inherent to a nonrandomized intervention study. However, this study can be considered a "natural experiment" study design. Although the natural experiments are more prone to bias than a randomized control trial, they are utilized when the randomized control trial is unethical or impractical, as in most surgical intervention research. The natural experiments have some strength that randomized control trial does not have. The results of this study design reflects, what happens when the results of a randomized control trial are implemented.[41]

Nonetheless, in the present analysis, using multicenter data of patients undergoing elective spine surgery with and without intrawound vancomycin application, at seven sites across the U.S., we demonstrated that the use of intrawound vancomycin significantly reduced the risk of overall SSI and SSI returning return to OR. The relatively large number of patients in each treatment group allowed a robust statistical analysis to derive a meaningful difference in the risk of SSI in patients without intrawound vancomycin application.

CONCLUSION

The intrawound application of vancomycin after spine surgery decreased (1) the risk of SSI; (2) return to OR due to SSI; and (3) SSI in patients previously shown to be high risk for SSI. An increased risk of returning to OR due to SSI was found in patients in whom intrawound vancomycin was not used, higher number of operated levels, and postoperative ICU stay. The application of local intrawound vancomycin is safe and has the potential to reduce health care resource utilization.

➢ Key Points

- ❑ Analysis of data from a prospective multicenter observational study was conducted.
- ❑ Intrawound application of vancomycin after posterior spine surgery was associated with a reduced risk of SSI and return to OR due to SSI.
- ❑ The risk of SSI and return to OR due to SSI was higher in patients with increased number of levels exposed and those admitted postoperatively to intensive care unit (ICU).

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