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Clinical Study

Does intrawound vancomycin powder reduce surgical site infection after posterior instrumented spinal surgery? A propensity score-matched analysis

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Abstract

BACKGROUND CONTEXT: Recent reports suggested that placing vancomycin powder into surgical wounds before closure can prevent surgical site infections (SSIs) in spinal surgery.
PURPOSE: The present study aimed to evaluate if intrawound vancomycin powder could prevent SSIs after spinal surgery with posterior instrumentation.
STUDY DESIGN: This is a multicenter retrospective cohort study using propensity score matching.
PATIENT SAMPLE: We reviewed all spinal surgeries performed with posterior instrumentation from July 2012 to December 2014 at 11 institutions among patients aged ≥15 years.
OUTCOME MEASURES: The incidence of SSIs was compared between patients who received intrawound vancomycin powder (vancomycin group) and those who did not (control group).
METHODS: Demographic and operative data and microbiological findings of SSI cases were analyzed. After a preliminary whole-cohort analysis, we performed one-to-one propensity score matching to adjust for the differences between the two groups and then compared the incidence of SSIs between the matched groups. No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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RESULTS: A total of 2,859 patients were included in the study. In the vancomycin and control groups (n=694 and n=2165, respectively), 12 (1.73%) and 21 (0.97%) patients developed SSIs, respectively, but the difference was not statistically significant (p=.10, chi-square test). During the propensity score-matched analysis, 507 pairs were analyzed. No significant change in the rate of SSIs was seen between the vancomycin and control groups (8 SSIs [1.58%] vs. 9 SSIs [1.78%], respectively; p=.81, chi-square test). Microbiological analysis revealed that 5 of 12 (42%) and 11 of 21 (52%) SSIs in the vancomycin and control groups, respectively, were caused by *Staphylococcus* (p=.72, Fisher exact test).

CONCLUSIONS: Intrawound application of vancomycin powder was not associated with a significant decrease in the incidence of SSIs after posterior instrumented spinal surgeries in a propensity score-matched analysis. However, the rate of infections caused by *Staphylococcus* species was lower in the vancomycin group.

Keywords: Local antibiotics; Posterior instrumentation; Propensity score matching; Spine surgery; Surgical site infection; Vancomycin powder

Introduction

Surgical site infections (SSIs) are one of the most serious complications of surgery and a common concern among surgical specialties. Surgical site infections are associated with high morbidity, mortality, and health-care costs [1,2]. Despite the ubiquity of prophylactic antibiotics and aseptic techniques, SSIs occur at a rate of 0.6%–12% in patients undergoing instrumented spinal surgery [3–8].

Staphylococcus aureus and *Staphylococcus epidermidis* are the most common organisms associated with SSIs [9,10]; therefore, the use of intrawound vancomycin is considered to reduce the frequency of SSIs by killing these gram-positive cocci. However, the results of published studies have been inconsistent [5,11–15]. Moreover, most published data have been based on observational before–after analyses at one center.

The purpose of the present study was to evaluate if local vancomycin powder could prevent SSIs after spinal surgery with posterior instrumentation in a large-scale multicenter study. We used propensity score matching to adjust for patient characteristics and operative data. We also analyzed which infectious organisms caused the SSIs to assess whether the distribution of infectious organisms changed through the use of intrawound vancomycin powder.

Materials and methods

Patient selection

We conducted a surveillance study of SSIs after spinal surgery from July 2012 to December 2014; all spinal surgeries performed at 11 hospitals were registered. We included patients aged ≥15 years who underwent surgeries with posterior instrumentation. We did not differentiate according to surgical site (cervical, thoracic, or lumbar spine), and included combination surgeries using the anterior and posterior approaches. Patients who underwent surgeries to treat infective pathologies (including extradural abscess and pyogenic discitis), those who underwent surgeries only for rod elongation, and those who did not provide consent to participate in the study were excluded. Each patient had undergone follow-up for a minimum of 1 year. The institutional review boards of the participating hospitals approved the present surveillance study, and informed consent was obtained from each patient.

Standard preoperative and postoperative systemic prophylactic antibiotic regimen

Patients received standard systemic antibiotic prophylaxis consisting of intravenous (IV) cefazolin before surgical incision and additional intraoperative IV cefazolin if needed [16,17]. Postoperative IV cefazolin was also used for at least 24 hours after surgery. If the patient was allergic to beta-lactams, clindamycin was administered instead. Other infrequently used intravenous antibiotics included fosfomycin, minomycin, piperacillin, and vancomycin.

Treatment and control cohorts

We grouped the patients into two cohorts. The vancomycin group consisted of patients who received 1 or 2 g of intraoperative vancomycin powder, spread throughout the local wound immediately before closure. The powder was placed directly on the implants and muscles. The control group consisted of patients who did not receive intrawound vancomycin powder. No cases lacked documentation of affirmative or negative usage of intrawound vancomycin. The decision to use vancomycin and the amount were based on the surgeon's preference.

Diagnostic evaluation

Surgical site infections were identified using the 1999 definitions of the Centers for Disease Control and Prevention [16]. We did not distinguish between the extent of the SSIs (superficial, deep, or organ or space) in the present study. All patients participating in the study underwent standard laboratory tests on admission to the hospital, including peripheral white blood cell counts, C-reactive protein levels, and a

complete urine analysis. Abnormal C-reactive protein levels were based on the cut-off value of each hospital (0.3–0.9 mg/dL). Bacterial identification and susceptibility testing for SSI cases were performed according to the 1999 guidelines of the Centers for Disease Control and Prevention [16].

Clinical parameters

Pre- and intraoperative data were collected for each patient. The documented risk factors for SSI included body mass index, American Society of Anesthesiologists physical status classification, diagnosis of diabetes mellitus, hemodialysis, current smoking habits, chronic steroid or other immunosuppressant use, and previous surgery at the same site. Pertinent operative details, including estimated blood loss, operating time, and emergency surgery, as well as the use of autologous bone grafting, endoscopy, microscopy, fluoroscopy, and biological clean rooms, were also collected.

Statistical analysis

During our preliminary analysis, we compared backgrounds and SSI rates of the vancomycin and control groups. The null hypothesis was that no difference would be found in the postoperative SSI rate between patients who were treated with intrawound vancomycin powder and those who were not. Because of marked differences in the observed characteristics between the two groups, we established a one-to-one matching model using propensity scores to make the two groups directly comparable. In this model, each patient in the vancomycin group was closely matched with a patient from the control group, according to the likelihood that they would receive intrawound vancomycin powder. To estimate the propensity score, we fitted a logistic regression model for the use of local vancomycin powder as a function of 18 variables, including patient characteristics and operative data (Table 1). The C-statistic for evaluating the goodness of fit was calculated. Each patient of the vancomycin group was matched with a patient from the control group with the closest estimated propensity on the logit scale within a specified range (≤0.25 of the pooled standard deviation of estimated logits) to reduce differences between treatment groups by at least 90%. If two or more patients in the control group met this criterion, then we randomly selected one patient for matching.

Table 1
Variables used to fit a logistic regression model to calculate propensity scores

Patient characteristics
Gender, age, BMI, ASA PS, diagnosis of DM, previous surgery of the same site
Smoking habit, current steroid use, hemodialysis, current immunosuppressant use
Operative details
EBL, operative time, emergency surgery
Use of autologous bone grafting, endoscope, microscope, fluoroscope, BCR

BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status classification; DM, diabetes mellitus; EBL, estimated blood loss; BCR, biological clean room.

During the descriptive analyses of unmatched and matched cohorts, we compared patient characteristics, operative data, and postoperative SSI rates. We used the chi-square test to compare nominal scales, except for data including an expected cell frequency ≤5; in these cases, the Fisher exact test was performed. The Mann-Whitney *U* test was used to analyze ordinal scales. The threshold for significance was set at $p<.05$. All statistical analyses were conducted using JMP, version 13 (SAS Institute Japan, Tokyo, Japan).

Results

Analysis of the whole cohort

Table 2 shows the characteristics of the initial study cohort of 2,859 patients before they were matched according to their propensity scores to receive intraoperative vancomycin powder. In the sample of unmatched patients, 694 patients (24.3%) received intrawound vancomycin powder (vancomycin group) and 2,165 patients (75.7%) did not (control group).

Patient characteristics and operative data were significantly different between the two groups. Patients who received intrawound vancomycin powder were significantly older, had more comorbidities such as diabetes mellitus or chronic kidney disease, were more likely to have had previous surgeries at the same site, and had longer surgeries with greater blood loss.

During the preliminary analysis of the unmatched cohorts, the vancomycin group had a higher SSI rate (n=12; 1.73%) than the control group (n=21; 0.97%; p=.10); however, this difference was not significant.

Analysis of the matched cohorts

Using one-to-one propensity score matching, 507 pairs of patients in the control and vancomycin groups were selected. Table 3 shows the characteristics of the matched cohorts. The C-statistic for the goodness of fit was 0.800 in the propensity score model. After matching, no statistically significant differences in patient characteristics and operative data were noted between the two groups.

In the matched cohorts, eight (1.58%) and nine (1.78%) patients in the vancomycin and control groups developed SSIs, respectively. Although the incidence of SSIs was lower in the vancomycin group than in the control group, the difference was not significant (p=.81, Fig. 1).

Microbiology

A total of 26 pathogens were detected in 33 SSI cases. Detailed descriptions of all SSIs are shown in Tables 4 and 5 for the vancomycin group and control group, respectively.

The most common organisms cultured in both groups were *Staphylococcus* species, including *S. aureus* (both methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* [MRSA]) and coagulase-negative staphylococci. The rate of

Table 2
Clinical and surgical data of unmatched patients

n=2,859	Vancomycin: 694 patients	Control: 2,165 patients	p
Characteristics			
Gender			
Male, no. (%)	326 (47.0%)	999 (46.3%)	
Female, no. (%)	368 (53.0%)	1,161 (53.8%)	.74
Age (mean), y	68.5	65.0	<.0001
American Society of Anesthesiologists physical status classification			<.0001
1	107 (15.9%)	370 (14.1%)	
2	452 (67.3%)	1,384 (52.7%)	
3	110 (16.4%)	200 (7.6%)	
4	3 (0.5%)	0	
BMI (mean)	23.2	23.5	.07
Diabetes mellitus	146 (21.1%)	225 (10.4%)	<.0001
Previous surgery of the same site	271 (39.0%)	346 (16.0%)	<.0001
Smoking habit	40 (5.8%)	213 (9.9%)	.001
Current steroid use	46 (6.6%)	98 (4.5%)	.03
Hemodialysis	43 (6.2%)	52 (2.4%)	<.0001
Immunosuppressant use	29 (4.2%)	48 (2.2%)	.006
Operative details			
EBL (mean), mL	759	458	<.0001
Operative time (mean), min	243	210	<.0001
Autologous bone grafting	124 (18.1%)	623 (28.9%)	<.0001
Endoscopy	26 (3.8%)	508 (23.5%)	<.0001
Microscopy	9 (1.4%)	9 (0.4%)	.007
Fluoroscopy	88 (12.7%)	907 (41.9%)	<.0001
Biological clean room	176 (25.4%)	733 (33.9%)	<.0001
Emergency surgery	53 (7.7%)	98 (4.5%)	.001
Outcomes			
SSI	12 (1.73%)	21 (0.97%)	.10

BMI, body mass index; EBL, estimated blood loss; SSI, surgical site infection.

Staphylococcus species in SSI cases was 42% (n=5) in the vancomycin group and 52% (n=11) in the control group (Fig. 2). These ratios were not significantly different between the two groups (p=.72, Fisher exact test). There were three MRSA infections in the control group and one MRSA infection in the vancomycin group.

The rate of gram-negative rods, mainly *Pseudomonas aeruginosa*, in SSI cases was higher in the vancomycin group (n=4; 33%) than in the control group (n=4; 19%). However, the rates were not significantly different between the two groups (p=.42, Fisher exact test).

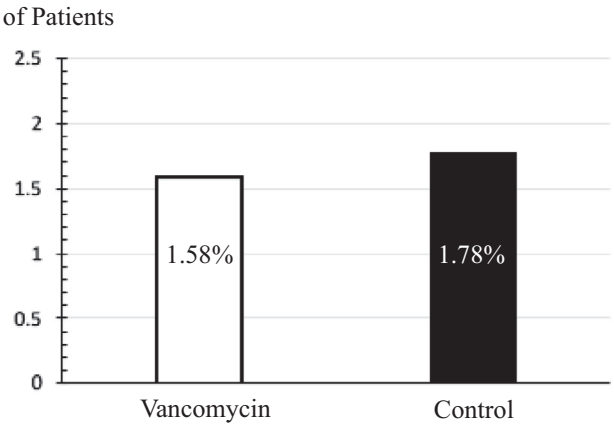

Fig. 1. Incidence of postoperative surgical site infections in patients who received and who did not receive intrawound vancomycin powder in the propensity score-matched cohorts.

Discussion

The use of intrawound vancomycin powder has rapidly spread among spinal surgeons since Sweet et al. [11] first reported its potential ability to decrease the incidence of SSIs after spinal surgeries. Ehlers et al. [5] reported that intrawound antibiotics were used in 55% of spinal fusion surgeries performed at 20 Washington State hospitals, despite the paucity of robust data supporting its use.

This multicenter retrospective cohort study aimed to assess if local intrawound vancomycin powder could prevent SSIs after posterior instrumented spinal surgeries using propensity score matching. Our data revealed that intrawound vancomycin powder did not result in a significant decrease in SSIs. These results are not consistent with those of most of the existing studies, which have reported decreased rates of postoperative SSIs with the use of intrawound vancomycin [11–15]. Three meta-analyses concluded that intrawound vancomycin powder was associated with a decreased risk of SSIs after spinal surgeries [18–20]. In contrast, two randomized controlled trials (RCTs) reported no significant changes in the rate of SSIs. Tubaki et al. [21] compared open spinal

Table 3
Clinical and surgical data of propensity score-matched patients

n=1,014	Vancomycin: 507 patients	Control: 507 patients	p
Characteristics			
Gender			
Male, no. (%)	234 (46.2%)	233 (46.0%)	
Female, no. (%)	273 (53.9%)	274 (54.0%)	.95
Age (mean), y	67.5	67.1	.99
American Association of Anesthesiologists physical status classification			.73
1	80 (15.8%)	81 (16.0%)	
2	348 (68.6%)	338 (66.7%)	
3	79 (15.6%)	88 (17.4%)	
4	—	—	
BMI (mean)	23.1	23.3	.22
Diabetes mellitus	92 (18.2%)	96 (18.9%)	.75
Previous surgery of the same site	150 (29.6%)	149 (29.4%)	.95
Smoking habit	26 (5.1%)	29 (5.7%)	.68
Current steroid use	33 (6.5%)	35 (6.9%)	.80
Hemodialysis	27 (5.3%)	26 (5.1%)	.89
Immunosuppressant use	25 (4.9%)	25 (4.9%)	1.00
Operative details			
EBL (mean), mL	678	652	.24
Operative time (mean), min	244	239	.23
Autologous bone grafting	84 (16.6%)	74 (14.6%)	.39
Endoscope	11 (2.2%)	9 (1.8%)	.65
Microscope	7 (1.4%)	4 (0.8%)	.36
Fluoroscope	66 (13.0%)	59 (11.6%)	.50
Biological clean room	148 (29.2%)	136 (26.8%)	.40
Emergency surgery	46 (9.1%)	47 (9.3%)	.91
Outcomes			
SSI	8 (1.58%)	9 (1.78%)	.81

BMI, body mass index; EBL, estimated blood loss; SSI, surgical site infection.

surgeries at any level with and without the use of intrawound vancomycin powder. In their RCT involving 907 patients, they found no statistically significant decrease in the rate of postoperative SSIs (vancomycin group 1.61% vs. control group 1.68%). Mirzashahi et al. [22] conducted another RCT that demonstrated a relative increase in SSI rates with the use of intrawound vancomycin (vancomycin group 5.2% vs. control group 2.7%; p=.2), although their method of applying vancomycin was not identical to that of previous studies. They applied vancomycin powder after closure of the fascia, whereas other studies reported that it was applied in the subfascial layer [11–15,23–25].

Similarly, some observational studies reported no significant decrease in the rate of SSIs with the use of intrawound vancomycin. Martin et al. [26] reported no significant decrease in the rate of deep SSIs (vancomycin group 5.1% vs. control group 5.3%; p=.936) in their observational study including 306 patients. Gaviola et al. [27] also reported similar

Table 4
Patient characteristics and microbiology reports of infected cases in the vancomycin group

Pt	Age	Gender	BMI	DM	Other risk factors	Operative time (min)	EBL (mL)	Primary causative organism
1	73	F	23.3	–	Previous surgery	155	240	MSSA
2	85	F	22.1	–		204	300	MRSA
3	71	F	16.4	–	Immunosuppressant and steroid use	239	450	MRCNS
4	60	F	21.3	–	Hemodialysis, previous surgery	234	415	MRCNS
5	75	F	21.1	–	Hemodialysis, previous surgery	215	300	MRCNS
6	68	F	21.9	–	Previous surgery	212	1,300	*P. aeruginosa*
7	71	M	26.1	–	Previous surgery	201	680	*P. aeruginosa*
8	74	M	28.7	–	Immunosuppressant and steroid use	181	350	*P. aeruginosa*
9	63	M	22.8	–	Previous surgery	144	440	*Enterococcus faecalis*
10	61	F	30.8	–		225	300	Anaerobic gram-negative bacilli
11	72	F	20.1	–	Steroid use, previous surgery	234	200	Unknown
12	76	F	20.3	–		199	50	Unknown

Pt, patient; BMI, body mass index; DM, diabetes mellitus; F, female; M, male; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MRCNS, methicillin-resistant coagulase-negative staphylococci; *P. aeruginosa, Pseudomonas aeruginosa*.

Table 5
Patient characteristics and microbiology reports of infected cases in the control group

Pt	Age	Gender	BMI	DM	Other risk factors	Operative time (min)	EBL (mL)	Primary causative organism
13	78	F	23.5	–		156	230	MSSA
14	78	F	24.2	–	Previous surgery	143	430	MSSA
15	75	F	17.8	–		230	400	MSSA
16	72	M	23.3	–	Smoking	475	1,430	MSCNS
17	15	M	14.8	–		290	735	MSCNS
18	38	M	43.8	–		449	850	MRSA
19	82	M	25.8	–	Previous surgery	302	300	MRSA
20	20	F	30.4	–		305	1765	MRSA
21	73	M	24.4	–		174	120	MRCNS
22	61	M	20.7	–	Previous surgery	343	256	MRCNS
23	72	F	20.4	–	Immunosuppressant and steroid use	640	750	MRCNS
24	76	M	24.6	+		547	1,300	*P. aeruginosa*
25	54	M	27.2	+	Hemodialysis, previous surgery	311	490	*P. aeruginosa*
26	81	F	24.7	–		162	100	*P. aeruginosa*
27	31	F	24.0	–	Previous surgery	789	1,520	*Enterobacter cloacae*
28	65	F	26.9	+		187	305	*Finegoldia magna*
29	58	M	21.2	–		188	400	Gram-positive bacilli
30	47	M	24.2	–	Smoking	167	1,979	Unknown
31	81	M	26.7	–		203	950	Unknown
32	78	F	15.3	–		204	110	Unknown
33	65	M	31.2	–		226	300	Unknown

Pt, patient; BMI, body mass index; DM, diabetes mellitus; F, female; M, male; MSSA, methicillin-susceptible *Staphylococcus aureus*; MSCSN, methicillin-susceptible coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MRCNS, methicillin-resistant coagulase-negative staphylococci; *P. aeruginosa*, *Pseudomonas aeruginosa.*

results (vancomycin group 5.2% vs. control group 11.0%; p=.08) in their observational study involving 326 patients.

However, these studies may lack statistical power owing to the relatively small number of patients. The estimated sample size needed for the RCT was approximately 4,600 participants. This number was based on the assumption that the SSI rate of the control cohort is 2.0% for posterior instrumented spinal surgeries [3], the rate of *Staphylococcus* species in SSI cases is 70% [9,10], and that two-thirds of staphylococcal infections are prevented by local application of vancomycin powder; consequently, the SSI rate of the vancomycin cohort was estimated to be 1.0%. In this estimation, we also assumed that the probability of falsely rejecting a true null hypothesis (α) was 0.05, and that the probability of failing to reject a false null hypothesis ($1 - \beta$) was 0.80.

Our preliminary analysis of the whole cohort showed a relative increase in the SSI rate in the vancomycin group (1.73% in the vancomycin group vs. 0.97% in the control group; p=.10). This was likely due to patients in the vancomycin group being at significantly higher risk of SSIs than

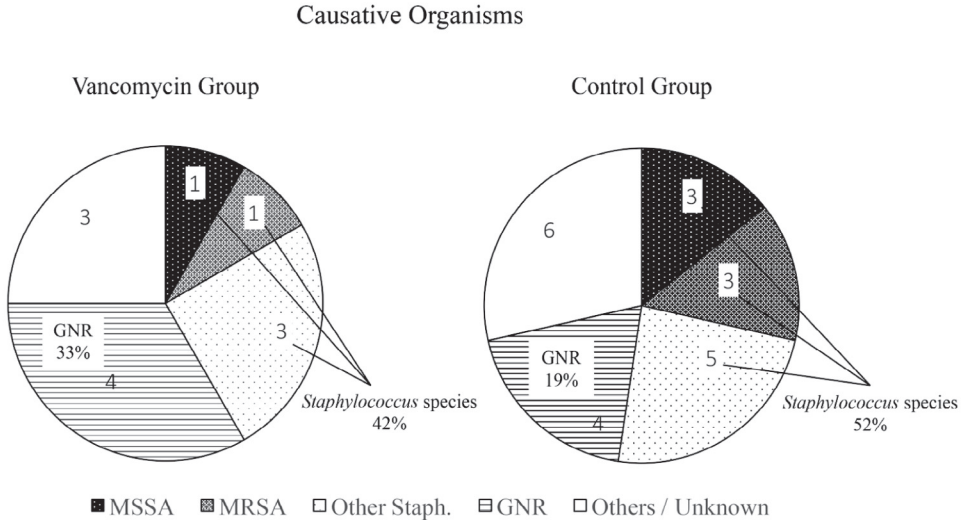

Fig. 2. Causative organisms in infected cases. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; Staph., *Staphylococcus* species; GNRs, gram-negative rods.

patients in the control group, as shown in Table 2. This difference could have resulted from most surgeons' preference of using intrawound vancomycin for high-risk populations.

To adjust for differences in patient characteristics and operative data between the two groups, we calculated propensity scores and established one-to-one matched cohorts. Patient parameters and surgical data were not significantly different between the two matched groups (p>.05 for each variable, Table 3). During the matched analysis, the vancomycin group showed a lower incidence of SSIs than the control group, but the difference was not significant (1.58% in the vancomycin group vs. 1.78% in the control group; p=.81). The sample size of our study might have been too small to detect whether vancomycin powder could prevent SSIs, although the estimation of the required sample size for propensity score matching is not considered the same as that for RCTs.

The decrease in the rate of infections by *Staphylococcus* species compared with all other infectious organisms in SSI cases in the vancomycin group in the present study (Fig. 2) might indicate the ability of vancomycin to prevent *Staphylococcus* infections. Conversely, the rate of infection caused by gram-negative rods increased in the vancomycin group. Other authors also reported comparable results for SSI-causative organisms [25,26]. The small increase in infections caused by gram-negative rods could have compensated for the decrease in *Staphylococcus* infections in the vancomycin group, thereby resulting in the absence of a significant change in the SSI rate caused by all pathogens through the use of intrawound vancomycin powder.

The present study was based on data collected prospectively in the surveillance study of SSIs. Therefore, it contains information regarding several potential risk factors for spinal SSIs, including current smoking habits and chronic steroid or other immunosuppressant use, as well as body mass index, American Society of Anesthesiologists physical status, diagnosis of diabetes mellitus, and hemodialysis. In the propensity score-matched analysis, all these factors were adjusted to ensure an even distribution in both groups. Nonetheless, there was no significant decrease in the SSI rate in the vancomycin group.

The present study had several limitations. First, we did not record the amount of applied vancomycin. Although the most commonly used dose of intrawound vancomycin is 1 g [13–15], some authors reported that they changed the dose according to the length of the incision [25]. The appropriate dose of vancomycin has not yet been determined. Second, we did not record some factors that might be associated with SSIs, such as the diagnosis of coronary heart disease, chronic obstructive pulmonary disease, or osteoporosis [8], and the surgeons' experience [28]. As these unrecorded factors cannot be adjusted via propensity score matching, they could have affected the SSI rates. This is a limitation attributable to the retrospective nature of the present study. Finally, the study did not include any patient-reported outcome scores, which might have been beneficial to the overall assessment of patients. A randomized, prospective study that includes patient-reported outcomes is needed.

Despite these limitations, our study indicates that the use of intrawound vancomycin powder does not reduce the incidence of postoperative SSIs in posterior instrumented spinal surgeries. Our data also suggest that the distribution of causative organisms might change with the use of intrawound vancomycin powder.

Conclusions

The intrawound application of vancomycin powder was not associated with a significant decrease in the rate of SSIs after posterior instrumented spinal surgery. The rate of infections by *Staphylococcus* species was lower in the vancomycin group than in the control group, but the difference was not significant. The small increase in infections caused by gram-negative rods could have compensated for the decrease in *Staphylococcus* infections in the vancomycin group, leading to the non-significant change in the overall SSI rate between the two groups.

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