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Clinical Study

Vancomycin powder mixed with autogenous bone graft and bone substitute may decrease the deep surgical site infections in elective lumbar instrumented fusion surgery for degenerative disorders: a prospective randomized study

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Abstract

BACKGROUND CONTEXT: Deep surgical site infections (DSSI) following lumbar instrumented fusion surgery are associated with considerable morbidity. Intraoperative application of vancomycin powder (VP) has been widely used to prevent DSSI; however, the effects of VP mixed with local autogenous bone graft (ABG) and bone substitute on DSSI prevention and bone fusion remains unclear.

PURPOSE: To examine the effects of VP mixed with ABG and bone substitute on DSSI and fusion rate.

STUDY DESIGN/SETTING: A prospective randomized case-controlled study at a single medical center. (ClinicalTrials.gov Identifier: NCT03883022).

PATIENTS' SAMPLE: Adult patients who underwent decompression along with instrumented fusion surgery for a degenerative lumbar condition were recruited from October 2017 to May 2023. Patients were randomly allocated to vancomycin (n=357) or control (without vancomycin) (n=348) groups. In the vancomycin group, 1 g of antibiotic powder was used for 2- and 3-level fusions (no 1 level fusions?) while 2 g was used for >3-level.

OUTCOMES MEASURES: The primary outcome was DSSI within 90 days after index surgery. Secondary outcomes included surgical and vancomycin-related complications, functional outcomes and bone fusion.

METHODS: All patients were followed up with plain spine radiographs at 1, 2, 3, 6, and 12 months after surgery. The definition of DSSI was based on the Centers for Disease Control and Prevention criteria for SSI. Posterolateral fusion was assessed using the Lenke criteria and interbody fusion was assessed using the Brantigan-Steffee-Fraser (BSF) definition. Solid fusion was defined as an angular change of <5° of the fused segments in supine dynamic flexion and extension lateral radiographs, Lenke grade A and B or BSF-3 definition. Antibiotic concentrations in the vancomycin group were measured in the serum and at the surgical site in the drain on days 1 and 3 after the index surgery. Functional outcomes were evaluated by Oswestry Disability Index (ODI) and visual analog scale (VAS) for leg pain.

FDA device/drug status: Not applicable.

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RESULTS: In total, 357 and 348 patients were enrolled in the vancomycin and control groups, respectively. Mean patient age was 67.7±11.0 years and 63.0% were female. There were no DSSIs in the vancomycin group and five in the control group (0 vs 1.4%, p=.029). All five patients with DSSI had diabetes (100%). None of the patients with diabetes in the vancomycin group developed DSSI (0/119 vs 5/105 in control group, p=.021). Postoperative serum vancomycin levels were undetectable and no vancomycin-related complications were observed. The mean vancomycin concentrations at surgical site in the drain were 524.5±209.9 μg/mL and 217.4±97.2 μg/mL on postoperative days 1 and 3, respectively (measured in a drain?). At the final follow-up, functional outcomes and bone fusion rates were similar between the two groups. Solid posterolateral fusion (Lenke grade A or B) was observed in 79.3% (257/324) of the vancomycin group and 73.5% (233/317) of the control group (p=0.348). Interbody fusion, based on the BSF-3 definition, was observed in 99.4% (326/328) of cages in the vancomycin group and 99.6% (258/259) in the control group (p=1.000). Based on the criteria of angular change of < 5° on dynamic lateral radiographs, the solid fusion rate was 100% in both groups.
CONCLUSIONS: Vancomycin mixed with local ABG and bone substitute maintains high vancomycin level at surgical site and appears safe and effective for preventing DSSI in lumbar degenerative instrumented fusion surgery without affecting bony fusion, especially in diabetic patients.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03883022.

Keywords: Autogenous bone graft; Bone substitute; Deep surgical site infection; Degenerative lumbar fusion surgery; Diabetes; Vancomycin

Introduction

Deep surgical site infections (DSSI) are serious complications of instrumented spinal surgery. In clinical practice, vancomycin is used to prevent infection after spinal surgery; however, its effects are contradictory. Some studies report that vancomycin significantly reduces DSSI incidence [1–4], whereas others report no significant difference in occurrence [5–9] The heterogeneity of these randomized trials, such as differences in surgical indications, anatomical locations for fixation, and instrumentation, may account for the conflicting results. However, the effect of vancomycin in preventing DSSI remains unclear.

Bone grafts and substitutes are recommended in fusion surgery to treat lumbar degenerative diseases [10]. Our previous ambispective study showed that local vancomycin impregnated with autogenous bone graft (ABG) and bone substitute was effective in preventing DSSI after lumbar instrumented fusion surgery [11]. Accordingly, we conducted a prospective randomized study to evaluate the effects of vancomycin powder (VP) impregnated with ABG and a bone substitute on DSSI after degenerative elective lumbar fusion surgery. The primary outcome was the occurrence of DSSI after the index surgery. Secondary outcomes were surgical- and vancomycin-related complications, functional outcomes, and bone fusion at the final follow-up.

Methods

Study design

This prospective randomized study enrolled patients treated for degenerative lumbar disease at our medical center from October 2017 to May 2023. The study is registered at ClinicalTrials.gov (NCT03883022). Inclusion criteria were degenerative lumbar disease diagnosis, failed conservative treatment for at least 3 to 6 months, and underwent both decompression and instrumented fusion. The exclusion criteria were: (1) treatment with decompression only; (2) treatment with minimally invasive surgery; (3) diagnosis of cancer or osteomyelitis; (4) presence of a vertebral fracture; (5) refusal to participate in the study; (6) dynamic fixation during the operation; and (7) death or loss to follow-up after discharge. Patients were randomly allocated to a vancomycin or nonvancomycin group using blocks of six and the website randomization.com. All instrumentation including transpedicle screws (Smartlock Omega, A-Spine Inc., New Taipei City, Taiwan) and/or transforaminal lumbar interbody fusion (TLIF) with a banana-shaped polyetheretherketone cage (Rainboo lumbar cage, A-SPINE, United Orthopedic Corporation, Taiwan) was approved by the National Health Insurance Administration.

All patients were followed up with plain spine radiographs at 1, 2, 3, 6, and 12 months after surgery. Supine dynamic flexion and extension lateral radiographs were made at 1-year follow-up to evaluate whether the instrumented level was fused. Patients' demographic information, surgical details, microbiology reports, fusion status, and functional outcomes, including Oswestry Disability Index (ODI) and visual analog scale (VAS) for leg pain, were recorded and analyzed before surgery and at the latest follow-up.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Review Board (2017-10-008A). Signed informed consent was obtained from all patients.

Sample size calculation

In our prior study [11], the rate of DSSI was 0% in the vancomycin group and 3.5% in the nonvancomycin group. We performed a two-tailed test with a type I error (α) set at 0.05 and statistical power (1-type II error) set at 0.95; the sample size was calculated by G. Power 3.1 using Fisher's exact test with 1:1 ratio. Based on the calculations, 300 patients were included in each group. To account for an estimated drop-out/loss to follow-up rate of 20%, we incorporated a 20% increase in sample size; thus, 750 patients were included in the study plan to ensure an adequate sample size.

Infection control

All patients underwent standard surgical site skin preparation with one skin scrub of 2% chlorhexidine followed by three scrubs of povidone-iodine. Loban 2 (3M Health Care, St. Paul, MN, USA) iodine drapes were used in all steps after skin preparation. Prophylactic antibiotic (1 g cephalosporin) was intravenously injected 30 minutes before surgery and redosed every 4 hours or when blood loss exceeded 1,000 mL during the index surgery. Clindamycin was administered to patients with beta-lactam allergies. After surgery, 1 g of cephalosporin was administered every 8 hours, and 80 mg aminoglycoside was administered every 12 hours for 3 days. Patients were treated with conventional open posterior decompression, instrumentation, and fusion with ABG from the bone chips of decompressed laminae and spinous processes, which were mixed with β-tricalcium phosphate bone substitute (ChronOS, DePuy Synthes, West Chester, PA, USA) at an approximately 1:1 volume ratio.

In the vancomycin group, 1 g VP (Gentle Pharmaceutical Co., Yunlin, Taiwan) was mixed homogeneously with a mixture of ABG and bone substitute for 2- or 3-level fusion, and 2 g was used for more than 3-level fusion. To prevent the vancomycin from being washed out by blood, the mixture was left undisturbed for at least 30 min before use to allow the VP to adhere adequately to the bone graft mixture.

Meticulous intraoperative irrigation was routinely performed with normal saline by using a pulsatile lavage system (Interpulse, Stryker Co., Kalamazoo, MI, USA) throughout the procedure in both groups. At least 6 L normal saline was irrigated using a pulsatile lavage system. Moreover, 900-1000 mL normal saline was also irrigated after each disc preparation for TLIF with a bulb syringe (PAHSCO, Pacific Hospital Supply Co. Ltd, Miaoli County, Taiwan) [12]. All wounds were closed in the same manner with a suction drainage tube left in place. Patients were encouraged to ambulate with an orthosis on the day after the index surgery. The drainage tube was removed when total amount was <100 mL per day.

Superficial and deep surgical site infections (SSI) were defined based on Centers for Disease Control and Prevention criteria [13]. When DSSI was suspected, magnetic resonance imaging of the lumbar spine was performed, and serum C-reactive protein (CRP) levels were measured. If the aforementioned examinations were consistent with DSSI, computed tomography (CT)-guided biopsy was performed, and a tissue specimen was sent for histopathological examination and culture. If DSSI was confirmed by either examination, intravenous antibiotics were administered based on the wound condition and clinical situation or until the CRP levels returned to <1 mg/dL (checked weekly). After discontinuation of intravenous antibiotics, oral antibiotics were administered for another 6 weeks after consultation with an infectious disease physician. If persistent discharge or pus was observed in the DSSI, reoperation with extensive irrigation and debridement was performed. Parenteral antibiotics were prescribed for superficial SSI.

Measurement of vancomycin concentration

Vancomycin concentrations in the vancomycin group were measured in the serum and at the surgical site on days 1 and 3 after the index surgery. Surgical site concentration was measured using drain fluid. Measurements were performed using Architect iVancomycin (Abbott, Wiesbaden, Germany) and Architect i1000 SR analyzer (Abbott Laboratories, North Chicago, IL, USA). The Architect iVancomycin is an *in vitro* chemiluminescent microparticle immunoassay used for the quantitative measurement of vancomycin in human serum or plasma.

Outcomes

The primary outcome was the occurrence of DSSI during follow-up. Acute DSSI was defined as an infection occurring within 90 days postoperatively, while chronic DSSI was defined as an infection occurring beyond 90 days after the surgery [14]. The secondary outcomes were superficial SSI, surgical complications, in-hospital outcomes, vancomycin-related complications, functional outcomes, and bone fusion. Surgical complications included blood loss, screw loosening, cage migration, and dural tears. The in-hospital outcomes included the duration of drainage and length of hospital stay. Functional outcomes were VAS score for leg pain and ODI determined before the operation and at last follow-up. Posterolateral fusion was assessed using the Lenke criteria [15], and interbody fusion was assessed using the Brantigan-Steffee-Fraser (BSF) definition [16]. Two experienced spine surgeons evaluated both fusion grades if any disagreements, which was discussed together to reach a consensus. Solid fusion was defined in the fusion group as an angular change of $< 5^{\circ}$ of the fused segments in supine dynamic flexion and extension lateral radiographs at 1-year follow-up [17]. Screw loosening was defined as a $\geq$ 1 mm radiolucent halo surrounding the screw [18].

Statistical analysis

Continuous data are presented as mean±standard deviation and compared using the Student's t-test. Categorical data are presented as counts and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. A paired t-test was used to examine the difference in vancomycin concentration from postoperative days 1 to 3. All analyses were two-sided, and $p<.05$ was considered statistically significant. All statistical analyses were performed using SAS software (version 9.4; SAS, Cary, NC, USA).

Results

A flow diagram of the patient selection process is shown in Figure. A total of 808 patients with degenerative lumbar disease were treated at our institution from October 2017 to May 2023. After excluding 54 patients who did not meet inclusion criteria, 754 patients were enrolled in the study and we stopped inclusion of additional patients. There were 49 patients that were subsequently excluded because of dynamic fixation, death, or loss to follow-up. Finally, 705 patients were included, with a mean follow-up of 44.2 months.

Baseline characteristics of the vancomycin and nonvancomycin groups are summarized in Table 1. The mean age was 67.7±11.0 years and 37.0% were male. No significant differences were observed in other characteristics between groups. Outcomes are summarized in Table 2. Mean blood loss was 684.9±424.5 mL, 16% of patients had screws that became loose, 3.8% had a dura tear, and none had cage migration. The mean drainage duration was 3.8±1.0 days, 6% of patients had a drain duration > 5 days, and the mean length of hospital stay was 9.2±5.0 days. The mean VAS leg pain score preoperatively was 5.7±1.8 and at follow-up was 1.5±0.8, and the mean ODI was 50.5±16.1 preoperatively and 16.7±6.0 at follow-up.

The overall incidences of deep and superficial SSI were 0.7% (5/705) and 1.4% (10/705), respectively. None of the patients in the vancomycin group (0/357) developed DSSI, whereas 1.4% (5/348) in the nonvancomycin group developed DSSI (p=.029). Moreover, seven (2%) and three (0.9%) patients had superficial SSI in the vancomycin and nonvancomycin groups, respectively (p=.341). All DSSI

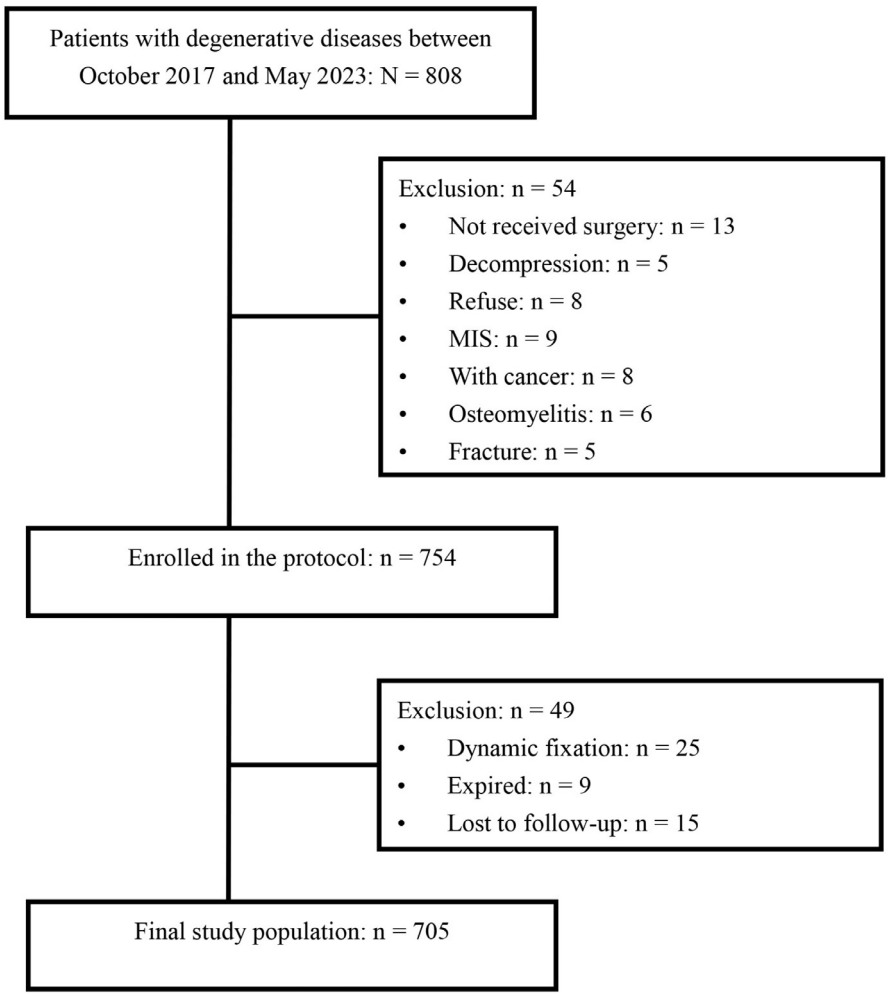

Fig. Flow diagram of patient inclusion. MIS, minimal invasive surgery.

Table 1
Baseline characteristics of the vancomycin and nonvancomycin groups

Variable	Total	Group		p-value
		Vancomycin	Nonvancomycin	
Number	705	357	348	
Sex, male	261 (37.0)	131 (36.7)	130 (37.4)	.856
Age	67.7±11.0	68.1±11.3	67.3±10.7	.306
BMI, kg/m^2	26.7±4.3	26.5±4.2	26.9±4.4	.218
BMI > 30, kg/m^2	143 (20.3)	63 (17.7)	80 (23.0)	.078
Smokers	104 (14.7)	55 (15.4)	49 (14.1)	.620
COPD	9 (1.3)	5 (1.4)	4 (1.1)	1.000
Diabetes	224 (31.8)	119 (33.3)	105 (30.2)	.367
Preoperative serum glucose level > 125 mg/dL	177 (25.1)	95 (26.6)	82 (23.6)	.351
RA	21 (3.0)	8 (2.2)	13 (3.7)	.243
ESRD	12 (1.7)	7 (2.0)	5 (1.4)	.591
ASA				.530
1	26 (3.7)	16 (4.5)	10 (2.9)	
2	486 (68.9)	245 (68.6)	241 (69.3)	
3	192 (27.2)	95 (26.6)	97 (27.9)	
4	1 (0.1)	1 (0.3)	0 (0.0)	
Revision	70 (9.9)	32 (9.0)	38 (10.9)	.385

Data are presented as mean±standard deviation or count (percentage).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; ESRD, end-stage renal disease; ASA, American Society of Anesthesiologists physical status.

occurred in the acute stage (within 3 months) (range, 8–88 days; Supplementary Table 1) following the index surgery. No late (>3 months) DSSI was observed in either group.

The differences between patients with and without DSSI in the nonvancomycin group are summarized in Table 3. All patients with DSSI had diabetes, and only 29% without

Table 2
Surgical outcomes between vancomycin and nonvancomycin groups

Variable	Total	Group		p-value
		Vancomycin	Nonvancomycin	
Number	705	357	348	
Surgical complications				
Blood loss, mL	684.9±424.5	681.3±425.5	688.6±424.0	.821
Screws loosening	112 (15.9)	59 (16.5)	53 (15.2)	.638
Cage migration	0			
Dura tear	27 (3.8)	15 (4.2)	12 (3.4)	.602
In-hospital outcome				
Drain duration > 5 days	40 (5.7)	23 (6.4)	17 (4.9)	.371
Length of hospital stay	9.2±5.0	9.5±5.4	8.9±4.6	.084
Functional outcome				
Preoperative VAS pain score at leg	5.7±1.8	5.7±1.8	5.6±1.9	.758
(Final VAS at leg)	1.5±0.8	1.6±0.8	1.5±0.9	.470
Change of VAS at leg	−4.1±2.0	−4.1±1.9	−4.1±2.1	.955
Preoperative ODI	50.5±16.1	50.5±16.0	50.5±16.2	.986
(Final follow-up ODI)	16.7±6.0	16.8±5.8	16.5±6.1	.522
Chang of ODI	−33.8±15.0	−33.7±14.4	−33.9±15.7	.814
SSI				
Deep SSI	5 (0.7)	0 (0.0)	5 (1.4)	**.029**
Acute stage (within 90 days)	5	0	5*	
Chronic stage	0	0	0	
Superficial SSI	10 (1.4)	7 (2.0)	3 (0.9)	.341

Data are presented as mean±standard deviation or count (percentage).

The significant result was shown in bold.

VAS, visual analogue scale; ODI, Oswestry disability index; SSI, surgical site infection.

* One 73-year-old male had deep SSI at 19 days after index surgery (Supplementary Table 1). He suffered from pneumonia at right lower lobe (RLL) with endotracheal intubation at 8 days after surgery and was expired 48 days after index surgery due to cardiopulmonary collapse and multiple organs failure in the ICU ward. The functional outcome and bone fusion for this patient were excluded.

Table 3
Comparison between patients with and without a deep SSI in the non-vancomycin group

Variable	Deep SSI		p-value
	Yes	No	
Number	5	343	
Sex, male/female	3/2	127 (37.0)	.366
Age	67.8±15.6	67.7±11.0	.983
BMI, kg/m^2	28.2±3.8	26.7±4.3	.436
BMI > 30 kg/m^2	2 (40.0)	78 (22.7)	.325
Smoker	1 (20.0)	48 (14.0)	.534
COPD	0 (0.0)	4 (1.2)	1.000
Diabetes	5 (100.0)	100 (29.2)	**.002**
Preoperative serum glucose level > 125 mg/dL	2 (40.0)	80 (23.3)	.337
RA	1 (20.0)	12 (3.5)	.174
ESRD	0 (0.0)	5 (1.5)	1.000
Five or more level fusion	0 (0.0)	28 (8.2)	1.000
Revision surgery	0 (0.0)	38 (11.1)	1.000
Number of cage insertions (of disc level)			.885
0	3 (60.0)	137 (39.9)	
1	2 (40.0)	124 (36.2)	
2	0 (0.0)	62 (18.1)	
3	0 (0.0)	19 (5.5)	
4	0 (0.0)	1 (0.3)	
Locations of cage insertions (311 cages)			
L1-2 level	-	-	-
L2-3 level	0 (0.0)	23 (6.7)	1.000
L3-4 level	0 (0.0)	75 (21.9)	.589
L4-5 level	2 (40.0)	169 (49.3)	1.000
L5-S1 level	0 (0.0)	42 (12.2)	1.000
Drain duration > 5 d	1 (20.0)	16 (4.7)	.223

Data are presented as mean±standard deviation or count (percentage).
The significant result was shown in bold.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; ESRD, end-stage renal disease; SSI: surgical site infection.

DSSI had diabetes (p=.002). Detailed information on the patients with DSSI is shown in Supplementary Table 1. DSSI rates in patients with diabetes in the two groups are compared in Table 4. Among the 224 patients with diabetes, the DSSI rate was significantly higher in the nonvancomycin group than in the vancomycin group (4.8% vs 0%, p=.021).

Vancomycin concentrations are summarized in Table 5. The vancomycin concentration in the drain significantly decreased from postoperative days 1 to 3 (p<.001). Moreover, vancomycin was undetectable in serum on postoperative day 1. No vancomycin-related side effects such as renal toxicity, ototoxicity, or red man syndrome (vancomycin flushing syndrome) were investigated during follow-up.

Table 4
Deep SSI rate of patients with diabetes in the vancomycin and non-vancomycin groups

Variable	Deep SSI	Group		Group p-value
		Vancomycin	Nonvancomycin	
Number	224	119	105	
Deep SSI	5 (2.2)	0 (0.0)	5 (4.8)	**0.021**

Data are presented as count (percentage).
The significant result was shown in bold.
SSI. surgical site infection.

Table 5
Vancomycin concentrations in the vancomycin group

Drainage fluid (μg/mL)	Mean	SD	p-value*
1st day	524.5	209.9	**<.001**
3rd day	217.4	97.2	
Serum at 1st day (μg/mL)	Undetectable		

The significant result was shown in bold.
SD, standard deviation.
* Paired t test.

The bone fusion rates in the two groups are shown in Table 6. There were 648 patients followed up for at least 1 year, and 654 cages were inserted into these patients, meanwhile bony fusion evaluated by Lenke classification and BSF definition in 587 cages. Based on the Lenke (p=.353) and BSF (p=1.000) classifications, no significant differences were observed in posterolateral and interbody fusion between the two groups, respectively. Solid posterolateral fusion (Lenke grade A or B) was observed in 79.3% (257/324) of the vancomycin group and 73.5% (233/317) of the control group (p=.348), respectively. Interbody fusion, based on the BSF-3 definition, fusion rates were observed in 99.4% (326/328) of cages in the vancomycin group and 99.6% (258/259) in the control group (p=1.000), respectively. None of the patients had an angular change greater than 5° at the index instrumentation level on dynamic flexion-extension radiographs.

Discussion

The primary finding of this prospective study was that local VP impregnated with ABG and bone substitute may be associated with a reduced DSSI incidence after elective lumbar instrumented fusion surgery for degenerative disease. There was no difference in bone fusion rates between the vancomycin and nonvancomycin groups, and no vancomycin-related side effects were observed.

The postoperative development of SSI can have serious consequences for patient recovery. Urquhart et al [19] studied the impact of SSI on outcomes after open posterior instrumented thoracolumbar surgery for degenerative disorders, in 79 patients who developed SSI and 456 who did not. Of the patients with infection, 31 had complicated infections and 48 had superficial infections. Patients with SSI had double the emergency room visit rate and additional surgery rate compared to those without an infection. Additionally, patients with SSI had poorer overall physical function.

Regarding the impregnation process, the optimal time and methods have not yet been established, and the method that ensures the highest level of antibiotic impregnation

Table 6
Bony fusion rates of the two groups*

Variable	Total	Group		Group p-value
		Vancomycin	Nonvancomycin	
Number	648	330	318	
Numbers of discs with cages inserted				**.038**
0	225 (34.7)	99 (30.0)	126 (39.6)	
1	247 (38.1)	133 (40.3)	114 (35.8)	
2	129 (19.9)	70 (21.2)	59 (18.6)	
3	39 (6.0)	21 (6.4)	18 (5.7)	
4	8 (1.2)	7 (2.1)	1 (0.3)	
Locations of cage insertions (654 cages: 364 vs 290)				
L1-2 level	5 (0.8)	5 (1.5)	0 (0.0)	.062
L2-3 level	52 (8.0)	30 (9.1)	22 (6.9)	.309
L3-4 level	169 (26.1)	98 (29.7)	71 (22.3)	**.033**
L4-5 level	343 (52.9)	185 (56.1)	158 (49.7)	.104
L5-S1 level	85 (13.1)	46 (13.9)	39 (12.3)	.528
Posterolateral fusion evaluated by Lenke Classification (641 patients: 324 vs 317)†				.348
A (Definite solid)	216 (33.7)	115 (35.5)	101 (31.9)	
B (Possibly solid)	274 (42.7)	142 (43.8)	132 (41.6)	
C (Probably not solid)	138 (21.5)	62 (19.1)	76 (24.0)	
D (Definitely not solid)	13 (2.0)	5 (1.5)	8 (2.5)	
Bony fusion evaluated by BSF definition (587 cages: 328 vs 259)†				1.000
BSF-1 (radiographic pseudarthrosis)	1 (0.2)	1 (0.3)	0 (0)	
BSF-2 (radiographic locked pseudarthrosis)	2 (0.3)	1 (0.3)	1 (0.4)	
BSF-3 (radiographic fusion)	584 (99.5)	326 (99.4)	258 (99.6)	

Data are presented as count (percentage).
The significant result was shown in bold.
BSF, Brantigan, Stefee, and Fraser.
* Patient operation dates were between October 2017 and October 2022.
† One patient who expired at 48 days after index surgery was excluded for fusion evaluation (Supplementary Table 1).

remains unclear [20]. Several previous in vivo and animal studies have reported effective impregnation durations ranging from 5 to 20 minutes [20–22]. The rationale for mixing for a while was to allow the vancomycin (a glycopeptide) to adhere to the microstructure of the bone graft, thereby minimizing washout from the wound, as reported by Sweet et al [22]. In our study, the time interval between completing the decompression and preparing for the instrumented fusion procedure typically exceeded 30 minutes. One in vitro study also revealed that the duration of time used for antibiotic impregnation of bone grafts had a profound influence on the subsequent release of antibiotics [23]. However, more in vitro and in vivo investigations are recommended to clarify the issue regarding the optimal manual mixing duration used for VP impregnation of bone graft.

The entire vancomycin protocol in this study included preoperative prophylactic antibiotics, intraoperative irrigation, intraoperative use of VP, and postoperative prophylactic antibiotics, based on our previous ambispective study [11]. Postoperative aminoglycoside was also part of the protocol to address specific concerns. First, widespread use of prophylactic intrawound vancomycin has been reported to potentially increase the incidence of gram-negative and polymicrobial DSSIs [24]. To counter this, postoperative aminoglycoside was prescribed to cover gram-negative bacteria and mitigate the risk of selective pressure. Second, as Long et al [25] noted, lumbar SSIs are more commonly caused by gram-negative and enteric bacteria compared to cervical SSIs, which are dominated by gram-positive pathogens. They suggested a broader antibiotic regimen for lumbar surgery, such as cephazolin and gentamicin, to improve gram-negative coverage. In our setting, gentamycin powder was unavailable for intra-wound application, necessitating its postoperative use. This prospective study design followed the original vancomycin protocol from our previous ambispective study [11], initiated in 2015. The protocol included a 3-day course of prophylactic antibiotics until drain removal, following the NASS guidelines [26]. Maciejczak et al [27] demonstrated that a 72-hour antibiotic prophylaxis regimen significantly reduced SSI incidence compared to single-dose regimens. Although recent studies suggest shorter prophylaxis durations [28,29], the 3-day regimen continues to be routinely employed in our clinical practice for instrumented lumbar fusion with drainage.

Our study showed that local VP impregnated with ABG decreased DSSI incidence in patients who underwent lumbar instrumented fusion surgery. Many studies examining whether vancomycin reduces DSSIs in patients undergoing spinal surgery have shown inconsistent results [2–9]. Reasons may include different vancomycin delivery methods, such as implants soaked in vancomycin solution [2,6],

intrawound application [4,5,7,8], or mixing with bone graft [11] and dosages in the application of vancomycin, and heterogeneity in the study population, for example, disease pathology such as degeneration, fracture, adult deformity correction, or spine metastasis, and mixed instrumented and uninstrumented patients [5–9].

A meta-analysis reported that the incidence of SSI was approximately 2% when vancomycin was applied locally during spine surgery and approximately 5% when vancomycin was not used [1]. While many studies have shown that vancomycin is effective in reducing the risk of SSI, other studies have shown no effect. Two randomized trials on the use of local vancomycin in spinal surgery found no difference in SSI rate between patients who did and did not receive vancomycin [6,7]. However, adult spinal deformity correction and metastatic tumor surgery were included in both studies [6,7]; therefore, the study population was heterogeneous and different from ours. We only enrolled patients with lumbar degenerative disorders who underwent instrumented fusion surgery, the most common surgical indication for instrumentation [30,31] and offered a more consistent study group to reduce the fundamental bias.

Salimi et al [5] also reported that local vancomycin did not reduce the SSI rate but did increase gram-negative infection rates. A meta-analysis by Grande et al [24] also showed that intrawound vancomycin may increase the incidence of gram-negative and polymicrobial SSIs. However, a systematic review of 21 studies with control groups found that VP significantly reduced the relative risk of developing an SSI (RR=0.55, 95% CI: 0.45–0.67, p<.0001) and did not significantly increase the risk of infection by gram-negative pathogens (RR=1.11, 95% CI: 0.66–1.86, p=.701) [32]. However, we did not observe the selective pressure of vancomycin in our study, which remains a major concern for physicians.

The overall DSSI rate was lower in our study (incidence: 0.7%, 5/705) than in other similar studies [2–9]. This may be partly because we used an optimal amount of normal saline for intrawound irrigation during the entire operation [12], as well as our vancomycin protocol. Irrigation of the surgical wound reduces its bacterial load, with a greater amount of irrigation solution expected to reduce the bacterial load to a greater degree; irrigation with normal saline ≥1,400 mL/hour reduces SSI risk after lumbar fusion surgery in patients with diabetes [12]. In our protocol, the surgical wound was irrigated using a battery-powered irrigation device at three different timepoints with a total volume of normal saline ≥6,000 mL, and for TLIF each intervertebral disc was further irrigated with normal saline ≥900 mL using a bulb syringe. We may not overemphasize the effect of our vancomycin protocol and more irrigation strategies [33] on DSSI prevention, because disinfection of the operating room and instruments, appropriate antibiotic administration [34], and maintenance of sterility during surgery are also critical for reducing DSSIs [35,36].

Our results showed that the local use of up to 2 g vancomycin is safe, and no severe side effects, such as red man syndrome with circulatory collapse and unstable hemodynamic status, renal toxicity, or ototoxicity, were observed because of higher local concentration at the surgical site. However, Iyer et al [37] recently reported that a 14-year-old girl developed vancomycin flushing syndrome after the use of 1 g vancomycin-impregnated bone graft. The child had a lower bone surface area, which may explain this rare complication. Mariappan et al [38] reported that a 52-year-old female with a metastatic tumor underwent T-10 vertebrectomy and T-8 to T-12 instrumentation with 1 g VP spreading over the dura mater, and vancomycin-related circulatory collapse occurred during wound closure. Zhang et al [39] reported that seven patients who underwent decompression and instrumented fusion surgery (five for lumbar spines and two for thoracic spines) had vancomycin-related circulatory collapse during and immediately after wound closure. Six patients topically used 1 g vancomycin, and one patient (BMI: 26.1, L-345 decompression, instrumentation, and fusion) who used 3 g vancomycin had hypoxic encephalopathy and remained comatose. However, Ghobrial et al [40] reported up to 6 g vancomycin could be administered through the subfascial and epifascial layers in rare cases without red man syndrome reported. The safe dosage of vancomycin topically used in spinal fusion surgery remains controversial. Richter et al [41] reported that vancomycin had direct relaxing effects on vascular smooth muscle and may influence vascular tone, thereby affecting microcirculation in a rat study, which may explain the mechanism of red man syndrome, with circulatory collapse due to local vancomycin use. Unfortunately, red man syndrome is still diagnosed clinically because there are no reliable serological or histopathological diagnostic criteria [42]. However, serum vancomycin concentrations were not measured in any of these studies.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was cultured from the wounds of three patients (60%) with DSSI in the nonvancomycin group. MRSA is the most common bacterial species involved in postoperative infections, and vancomycin is effective against MRSA. The minimum inhibitory concentration (MIC) of vancomycin against MRSA is 0.5–4 mg/L, and the minimum bactericidal concentration against MRSA is 4–128 mg/L [42,43]. An in vivo study showed that the local half-life of vancomycin in total hip arthroplasty is 7 hours [44]. Thus, it is estimated that it takes up to 64 hours (approximately 3 days) for vancomycin to drop below MIC of 2 mg/L. ABG can be considered a local drug delivery system in which the drug is released slowly while the local concentration remains high [45]. Sweet et al [46] reported that with the local application of 2 g VP during thoracolumbar spine fusion surgery, the vancomycin concentration in the drainage fluid was 462 μg/mL on postoperative day 1 and 128 μg/mL on day 3. Our results are consistent with those of the aforementioned studies. The vancomycin concentration at the surgical site

on postop day 3 still exceeded the MIC of 2 mg/L. Accordingly, the advantages of using ABG as a local vancomycin delivery system include a slower release and higher local concentration maintenance at the surgical site.

Few studies have examined the clinical effects of vancomycin on bone fusion. Our results revealed that the local use of VP did not affect posterolateral or interbody fusion at 1-year follow-up regardless of the high local vancomycin concentration at the surgical site. This is important because vancomycin inhibits osteoblast proliferation *in vitro* [47] and reduces the fusion rate of demineralized bone matrix grafts in a rabbit model of spinal fusion [48]. In another study using a rabbit model of spinal fusion, the application of VP mixed with grafts reduced fusion rates by 30%; however, this only occurred at a concentration five times higher than that typically used by the authors [49].

While the use of vancomycin appears to reduce the risk of SSI in patients undergoing lumbar instrumented fusion surgery for degenerative diseases, it is not clear whether it is necessary for routine use in all surgically treated patients [50]. In patients without risk factors for DSSI, intrawound irrigation with large amounts of normal saline leads to good infection control for superficial SSI [12]. In our vancomycin protocol, the superficial SSI rates were similar between the two groups because vancomycin did not spread above the fascial layer. In future prospective randomized studies, we might use vancomycin separately at both the subfacial and suprafacial layers to prevent deep and superficial SSI simultaneously. However, for patients with relevant risk factors, especially diabetes, the application of vancomycin along with intrawound irrigation appears to reduce the risk of DSSI, based on our results and those of Hsiung et al [12]. We may conduct another prospective randomized study to evaluate additional local antibiotics for DSSI prevention against gram-negative and polymicrobial bacteria. Hopefully, we may formulate antibiotic stewardship algorithms and choose appropriate patients for local use of antibiotics to achieve the optimal goal of zero infections.

Limitations

This study has several limitations. First, complete follow-up of bone fusion should be performed for at least 2 years. Second, the cohort was from a single center and not multiple centers. Third, follow-up CT was not routinely arranged for fusion evaluation because of cost reduction, reduced radiation exposure, artifacts caused by metallic implants, and the policy of Taiwan's National Health Insurance.

Conclusions

VP mixed with ABG and bone substitutes in lumbar instrumented fusion surgery for degeneration may reduce the risk of DSSI, particularly in patients with diabetes. Moreover, neither bone fusion disturbance nor vancomycin-related toxicity was observed at 1-year follow-up, with a maximum of 2 g of vancomycin topically administered at the surgical site.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Shih-Tien Wang: Writing – review & editing, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Hsi-Hsien Lin:** Validation, Data curation. **Yu-Cheng Yao:** Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation. **Nicole Huang:** Validation, Supervision, Software, Methodology, Formal analysis. **Wei Hsiung:** Writing – original draft, Software, Resources, Investigation, Data curation. **Ming-Chau Chang:** Validation, Supervision. **Chien-Lin Liu:** Supervision. **Po-Hsin Chou:** Writing – original draft, Supervision, Project administration, Methodology.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2025.05.001.

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