Randomised Controlled Trial

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Safety and efficacy of intrawound vancomycin powder in the prevention of lumbar surgical site infection: a prospective, double-blind, randomized controlled study

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Background: To evaluate the safety and efficacy of intrawound vancomycin powder in reducing surgical site infections (SSIs) after spine surgery.
Design: A prospective, double-blind, randomized controlled study.
Participants: Patients who underwent posterior lumbar interbody fusion (PLIF) surgery from May 2021 to September 2022.
Methods: Patients who underwent PLIF surgery between May 2021 and September 2022 were included. Participants were randomized to the vancomycin treatment or control groups using block randomization (block size 4). Except for baseline and surgical data, the plasma levels of white blood cells, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aspartate aminotransferase, alanine aminotransferase, and serum vancomycin concentration in the groups were analyzed on postoperative days (PODs) 1, 3, and 5. Vancomycin concentration was measured daily until the drainage tubes were removed. The primary outcomes were the 90-day vancomycin-related adverse reactions and SSI rates. Secondary outcomes were perioperative hematological parameters and vancomycin serum (drain) concentrations.
Results: A total of 156 participants (78 each in each group) were analyzed by an independent researcher. The follow-up rate was 91%. All participants were followed up for at least 90 days. The 90-day SSI rate in the vancomycin group was 1.3% (1/78), comprising one case of superficial infection. The SSI rate in the control group was 10.3% (8/78), comprising seven cases of superficial infection and one case of deep infection. Compared with that in the control group, the SSI rate in the vancomycin group was decreased by 87.5%, with a statistically significant difference (RR = 0.125, 95% CI = 0.016–0.976). Additionally, the vancomycin group demonstrated a statistically significant decrease in serum ESR on POD 3 ($P = 0.039$) and CRP on POD 5 ($P = 0.024$) compared to the control group. The local plasma concentration of vancomycin remained elevated for at least 4 days postoperatively, while the serum concentration of vancomycin remained low. Vancomycin-associated adverse reactions were not observed.
Conclusion: Intrawound application of vancomycin powder is a safe and effective procedure for reducing the risk of SSI during PLIF surgery.

Keywords: efficacy, lumbar, safety, surgical site infection, vancomycin

Background

Surgical site infections (SSIs) represent a significant complication following spinal instrumentation surgery, resulting in elevated hospital expenses, extended hospital stay duration, diminished patient satisfaction, and increased morbidity and mortality rates[1]. Despite the use of prophylactic antibiotics and aseptic procedures, the incidence of SSIs varies between 0.7 and 16%[2,3].

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Intravenous antibiotics, including second-generation cephalosporins, are extensively utilized for perioperative prophylaxis in spine surgery owing to their robust efficacy against gram-positive bacteria, which are predominantly responsible for spinal SSIs[4].

Nevertheless, with the increased resistance to commonly used antibiotics, intravenous cephalosporins are reportedly ineffective against over 50% of the organisms known to cause SSIs[5]. Moreover, the number of complex cases of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has markedly increased[6].

Intrawound administration of vancomycin powder ensures the direct introduction of the antibiotic to the surgical site at high concentrations while limiting systemic absorption. Initially employed in cardiothoracic surgeries, this approach is effective in decreasing the incidence of SSIs[7,8]. Since then, several studies have indicated the use of vancomycin powder in orthopedic surgery[9–11]. However, most of these studies utilized a retrospective design. Additionally, the research thus far has lacked a uniform standard for defining SSIs and a dearth of laboratory data necessary for assessing the adverse effects and antimicrobial efficacy of topical vancomycin. Moreover, the pharmacokinetics of vancomycin *in vivo* when applied topically remains to be elucidated.

This study aimed to evaluate the safety and efficacy of the application of intrawound vancomycin powder in reducing the occurrence of SSIs and compare the findings with those of the exclusive use of intravenous prophylactic antibiotics among patients who underwent posterior lumbar interbody fusion (PLIF) surgeries.

HIGHLIGHTS

- A prospective, double-blind, randomized controlled study with 156 patients enrolled.
- Intrawound use of vancomycin decreases the infection rate by 87.5% compared with using intravenous prophylactic antibiotics alone.
- The intrawound application of vancomycin powder delivers a high concentration of the antibiotic to the surgical site and minimizes systemic absorption.
- No vancomycin-related adverse effects occur during follow-up.

Methods

Study design

This was a prospective, double-blind, randomized controlled study involving patients who underwent PLIF surgery and received intrawound vancomycin powder treatment. All patients were informed about the study design and consented to participate. This study was approved by the Medical Science Research Ethics Committee of our hospital, and the manuscript was written in accordance with the CONSORT guidelines for reporting randomized controlled trials[12].

Primary hypothesis

Compared to the conventional management group, the topical vancomycin would demonstrate lower rates of postoperative SSIs. In addition, the two groups would exhibit no notable difference in the frequency of adverse effects.

Participant recruitment

This study included 172 individuals diagnosed with degenerative lumbar disease who underwent PLIF surgery between May 2021 and September 2022 (Table 1). The inclusion criteria encompassed: (1) severe symptoms stemming from degenerative lumbar spine disorders; (2) instances of lumbar instability or marked lumbar disc degeneration, classified as above grade III according to the Pfirrmann classification; (3) lack of success with conservative treatments; (4) provision of informed consent; and (5) a minimum follow-up period of 90 days. The exclusion criteria include (1) impaired liver or kidney function; (2) allergies to cephalosporins or vancomycin; (3) recent glucocorticoid use; (4) presence of local or systemic infectious diseases; (5) psychological disorders, alcohol dependency, or a history of substance abuse; (6) pregnancy; and (7) hearing impairments. Sixteen participants were lost to follow-up, resulting in a follow-up rate of 91%. Finally, a total of 156 patients were included in the analysis (Fig. 1).

Patient and public involvement

The patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

Randomization

The attending physicians directly approached individuals diagnosed with degenerative lumbar disease who satisfied the specified inclusion and exclusion criteria and requested them to participate in the study. Eligible and consenting patients were randomly allocated (in a 1:1 ratio) to either the vancomycin treatment group or the control group using a block randomization method (block size of four) facilitated by a computer-generated randomization list. Details regarding group allocation were secured in opaque, sealed envelopes, which were managed by members of the study team who did not engage in direct clinical interactions with the participants to maintain the integrity of the blinding process. These envelopes, marked according to random number tables, were

Table 1

Baseline characteristics of patients.

Variable	Vancomycin group ($n=78$)	Control group ($n=78$)	*P*
Age (years)	59.3 ± 13.27	62.9 ± 8.63	0.09
Sex (female), *n* (%)	44 (56)	43 (55)	0.91
Height (m)	163.6 ± 6.95	164.7 ± 8.12	0.49
Weight (kg)	71.1 ± 11.22	69.0 ± 11.58	0.39
Comorbidities, *n* (%)			
Hypertension	39 (50)	47 (60)	0.26
Diabetes	16 (21)	21 (27)	0.45
Smoking	4 (5)	11 (14)	0.18
Diagnosis, *n* (%)			
Lumbar spinal stenosis	54 (69)	46 (59)	0.37
Lumber spondylolisthesis	15 (19)	18 (23)	0.56
Lumbar disc herniation	9 (11)	14 (18)	0.26

(Values are presented as mean ± SD or *n*%).

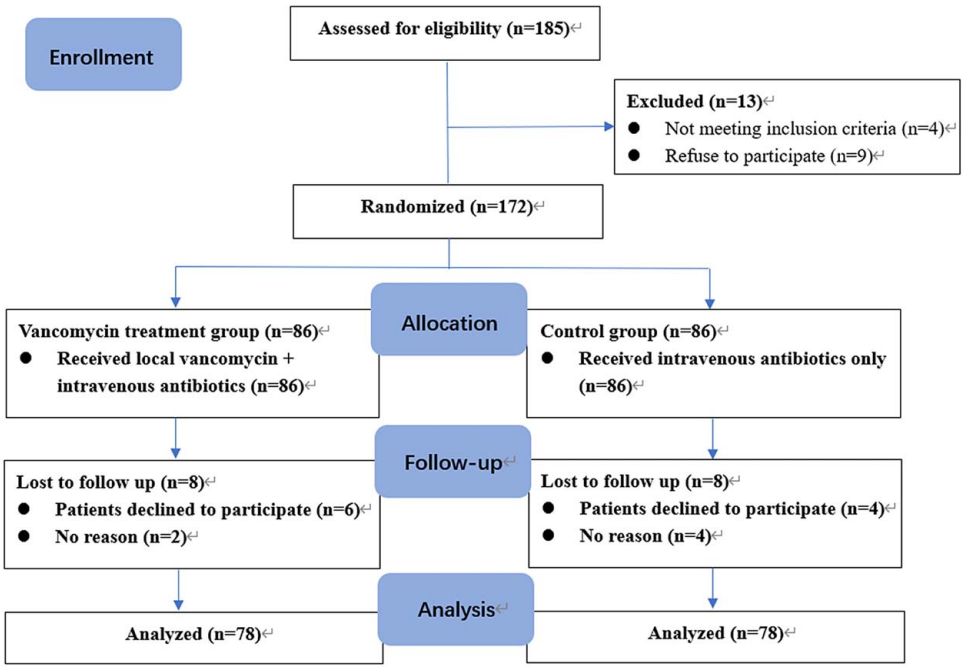

Figure 1. Patient randomization flowchart.

distributed to the enrolled patients sequentially, utilizing an interactive voice response system. Assignment to either trial group was undisclosed to the patients and the sponsors of the study. Owing to the noticeable distinctions in the surgical procedure, surgeons were not blinded to group assignments.

Perioperative infective control and surgical procedures

According to the Centers for Disease Control and Prevention (CDC) Guideline for the Prevention of Surgical Site Infection 2017, patients were instructed to shower at least the night before the surgery[13]. Each patient was required to rinse thoroughly and

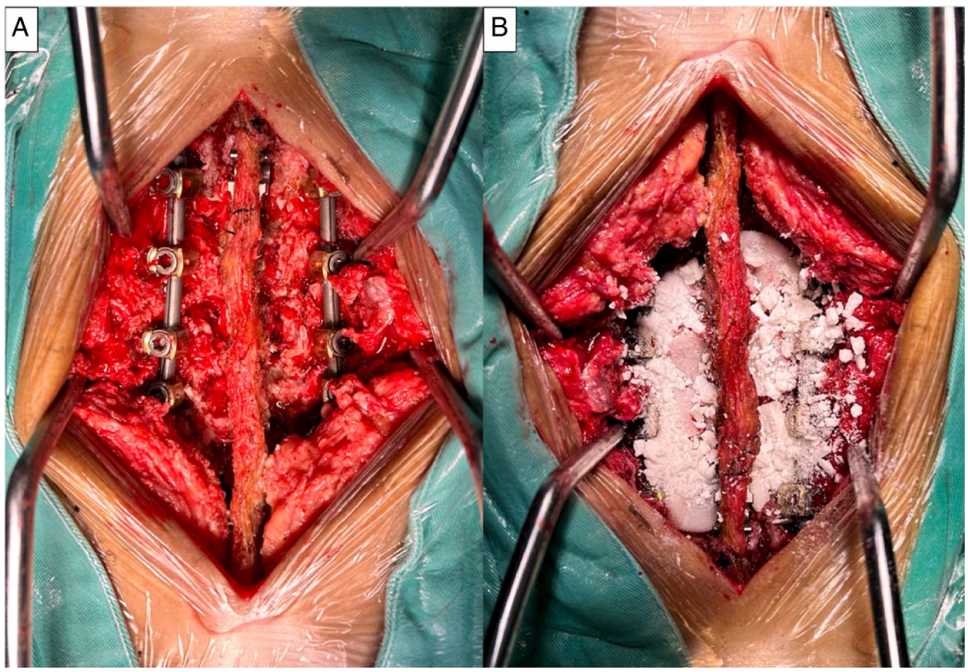

Figure 2. Surgical site photograph of posterior lumbar interbody fusion. (A) A patient with lumbar spinal stenosis underwent posterior lumbar interbody fusion from L2 to L5, and an interlaminar dynamic device was inserted between L1 and L2. The photograph shows the surgical site and the internal fixations before wound closure. (B) Vancomycin powder was locally applied in the vancomycin group.

Table 2

Comparison of perioperative characteristics between vancomycin and control group.

Variable	Vancomycin group (78 cases)	Control group (78 cases)	*P*
Preoperative blood glucose (mmol/l)	5.58 ± 2.12	5.27 ± 1.52	0.45
POD1 blood glucose (mmol/l)	5.79 ± 1.01	6.54 ± 2.81	0.34
Fusion levels	2.65 ± 0.83	2.80 ± 1.62	0.56
Mean intraoperative blood loss (ml)	250 ± 172.17	251 ± 113.07	0.97
Blood transfusion Rate (*n*, %)	22(28)	22(28)	1.00
Operation time (min)	189 ± 74.70	209 ± 75.07	0.20
Postoperative drains duration (days)	2.72 ± 0.89	2.65 ± 1.25	0.77

(POD: Post Operation Days; Fusion levels were defined as the number of intervertebral spaces from upper instrumented vertebra to lower instrumented vertebra).

freely, lather using an antiseptic soap, and rinse again. The patient was instructed to dry with a clean towel and wear a clean nightgown after showering. Blood glucose levels of patients with diabetes were monitored before surgery, and those with poor blood glucose control were consulted with endocrinology to control blood glucose. Intravenous cefuroxime (1.5 g) was administered within 1 h before the surgical incision; if the surgical procedure lasted for more than 3 h, another 1.5 g of intravenous cefuroxime was administered. Before the surgery, skin disinfection was performed according to a standardized protocol. The protocol involved applying one coat of tincture of iodine followed by two coats of 75% alcohol for skin antisepsis. A skin incision measuring ~5–8 cm was made on the lumbar spine, and muscles were separated layer by layer to expose the surgical site (Fig. 2). Forced-air warming was used to maintain intraoperative temperature.

All surgical procedures were performed by the same team of surgeons, ensuring no technical variances between the two groups. Following surgery and before wound closure, the surgical site was cleansed with a 0.9% saline solution. For patients within the vancomycin group, 1 g of vancomycin powder was applied over the muscle, fascia, and subcutaneous layers before suturing the skin. Drainage tubes were placed for all procedures, and the wound was closed in layers using absorbable sutures. After skin closure, the incisions were sterilized using alcohol and secured using sterile dressings. The dressings were replaced every 3 days, and the drainage tube remained in place until the total drainage was less than 50 ml over a 2 h period.

Outcome measures

Follow-up appointments for all patients were scheduled at 2 weeks, 1 month, 2 months, and 3 months postdischarge. The primary endpoints of this study included the incidence of vancomycin-related adverse reactions and SSI rates within 90 days, comparing the outcomes between the vancomycin treatment and control groups.

Vancomycin-associated adverse reactions included nephrotoxicity, hypotension, osteoblast toxicity, ototoxicity, and hypersensitivity reactions that occurred after intrawound application of vancomycin. SSIs were classified as superficial, deep, and space/organ infections. In this study, we defined SSIs according to the 2019 CDC National Healthcare Safety Network Patient Safety Manual[14]. Superficial infection was defined as an infection affecting only the skin and subcutaneous tissue of the incision site within 30 days following surgery, characterized by at least one of the following criteria: (1) clinical signs such as redness, warmth, tenderness, or localized swelling at the affected area; (2) a positive culture result from a specimen obtained under aseptic conditions; or (3) purulent discharge from the superficial incision. Deep infection was defined as an infection involving the fascial and muscle layers, manifesting within 90 days postsurgery. Space/organ infection was defined as any infection deeper than the fascial/muscle layers that were exposed or manipulated during the surgical process, identifiable within 90 days after the procedure through clinical symptoms, histopathological findings, or diagnostic imaging[14]. In cases where deep or space/organ infection was suspected, surface ultrasonography was performed for differentiation[15].

Secondary outcomes included perioperative hematological parameters and serum (drain) vancomycin concentrations. The plasma levels of white blood cells (WBCs), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum level of vancomycin were analyzed every 2 days after surgery, and the drain vancomycin concentration was measured every day until the drainage tube was removed.

Quality control measures during this clinical study

Detailed baseline data of all patients who met the inclusion and exclusion criteria, including those who opted out of the clinical trial, were meticulously recorded to mitigate selection bias. Standard operating procedures were established prior to the commencement of the trial. These included the dosage specification, precise location of drain placement, and timing of the

Table 3

Etiology of postoperative infection between vancomycin and control group.

	P. aeruginosa	E. coli	Klebsiella Spp.	S. aureus	Streptococcus pneumoniae	Total
Vancomycin group						
Superficial infection	1	—	—	—	—	1
Deep infection	—	—	—	—	—	—
Space/organ infection	—	—	—	—	—	—
Control group						
Superficial infection	—	1	1	2	1	5
Deep infection	—	1	—	—	—	1
Space/organ infection	—	—	—	—	—	—
Total	1	2	1	2	1	7

Table 4

Perioperative laboratory findings between vancomycin and control group.

Variable	Time	Vancomycin group	Control group	P
WBC(*10^9/l)	Baseline	7.32 ± 1.83	6.97 ± 1.75	0.42
	POD 1	9.98 ± 2.61	9.48 ± 2.67	0.37
	POD 3	7.15 ± 1.85	8.98 ± 2.63	0.00*
	POD 5	7.11 ± 1.95	8.43 ± 2.61	0.03*
NE% (%)	Baseline	63.48 ± 11.75	59.97 ± 8.68	0.12
	POD 1	83.18 ± 9.14	80.79 ± 15.91	0.38
	POD 3	70.4 ± 12.2	75.8 ± 9.37	0.02*
	POD5	70.17 ± 8.64	71.51 ± 11.23	0.60
RBC (*10^{12}/l)	Baseline	4.51 ± 0.53	4.48 ± 0.42	0.74
	POD 1	3.80 ± 0.53	3.80 ± 0.44	0.98
	POD 3	3.67 ± 0.57	3.62 ± 0.41	0.65
	POD 5	3.67 ± 0.46	3.64 ± 0.49	0.81
HGB (g/l)	Baseline	139 ± 18.7	133 ± 25.5	0.27
	POD 1	117 ± 18.0	121 ± 31.3	0.46
	POD 3	113 ± 17.8	111 ± 12.5	0.67
	POD 5	112 ± 15.6	111 ± 14.0	0.79
PLT (*10^9/l)	Baseline	238 ± 53.1	234 ± 72.1	0.76
	POD 1	197 ± 42.9	189 ± 56.1	0.44
	POD 3	199 ± 49.1	203 ± 63.4	0.70
	POD 5	245 ± 66.8	254 ± 79.8	0.64
ESR (mm/h)	Baseline	-	-	-
	POD 1	7.00 ± 6.18	6.07 ± 3.69	0.63
	POD 3	18.33 ± 15.15	26.14 ± 18.39	0.04*
	POD 5	34.41 ± 22.56	32.58 ± 19.37	0.75
CRP (mg/dl)	Baseline	-	-	-
	POD 1	2.74 ± 2.96	3.01 ± 2.09	0.78
	POD 3	4.36 ± 4.94	5.09 ± 4.21	0.49
	POD 5	3.00 ± 3.13	6.15 ± 6.02	0.02*
AST (U/l)	Baseline	20.4 ± 10.2	19.0 ± 3.98	0.38
	POD 1	24.4 ± 8.66	24.2 ± 8.43	0.95
	POD 3	23.5 ± 11.6	19.6 ± 6.56	0.17
	POD 5	38.0 ± 53.7	22.0 ± 14.0	0.29
ALT (U/l)	Baseline	22.3 ± 14.5	18.5 ± 6.84	0.12
	POD 1	19.6 ± 10.4	21.0 ± 10.0	0.59
	POD 3	22.9 ± 13.5	17.8 ± 7.58	0.13
	POD 5	29.5 ± 31.9	19.2 ± 9.62	0.25
TBIL (μmol/l)	Baseline	14.5 ± 6.87	13.4 ± 4.81	0.35
	POD 1	15.5 ± 6.45	14.2 ± 4.86	0.40
	POD 3	12.3 ± 5.63	14.5 ± 7.85	0.30
	POD 5	9.86 ± 3.68	12.0 ± 4.20	0.16
INBIL (mmol/l)	Baseline	10.1 ± 5.19	9.26 ± 3.14	0.32
	POD 1	10.2 ± 4.64	9.45 ± 3.62	0.44
	POD 3	8.07 ± 3.93	9.16 ± 4.90	0.42
	POD 5	6.99 ± 2.14	7.65 ± 2.74	0.48
CREA (μmol/l)	Baseline	64.2 ± 13.0	64.2 ± 17.6	1.00
	POD 1	62.7 ± 16.7	58.2 ± 17.9	0.32
	POD 3	62.7 ± 16.7	58.2 ± 17.9	0.74
	POD 5	60.5 ± 14.2	60.5 ± 14.2	0.84
BUN (mmol/l)	Baseline	6.87 ± 7.79	5.73 ± 1.35	0.35
	POD 1	5.21 ± 1.54	6.37 ± 7.94	0.40
	POD 3	7.66 ± 12.2	5.69 ± 7.94	0.49
	POD 5	5.11 ± 1.17	4.22 ± 1.68	0.28

ALT, Alanine Aminotransferase; AST, Aspartate aminotransferase; BUN, Urea Nitrogen; CREA, Creatinine; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; HGB, Hemoglobin; INBIL, Indirect Bilirubin; PLT, Platelet; POD, Post Operation Days; RBC, Red Blood Cell; TBIL, Total Bilirubin; WBC, White Blood Cell; NE%, Neutrophil%.

*$P < 0.05$, a significant difference.

application of intrawound vancomycin powder, which was determined by the researchers involved in all phases of the clinical trial. Additionally, the methods for data recording and the criteria for evaluation were standardized across the study. All observations and findings were rigorously verified to guarantee the integrity and reliability of the data. The conclusions drawn from the clinical trial were based directly on the collected original data. Throughout the trial and during data processing, stringent data management protocols were adhered to, ensuring the accuracy and validity of the outcomes.

Sample size and statistical analyses

In the present study, we hypothesized that 'the vancomycin group' was superior to 'the control group' in demonstrating reduced SSI rate. Power Analysis and Sample Size Software 19.0 was used to determine the required sample size. In a previous study, the SSI rate among patients who underwent PLIF was ~10.9%, and the infection rate decreased to 2.6% with the use of vancomycin. The sample size required for each group was calculated to be 73 cases, considering $\alpha = 0.05$, $\beta = 0.2$, and a 15% loss-to-follow-up rate, at least 86 participants were required for each group. Therefore, at least 172 patients were required for the statistical analysis.

All statistical analyses were performed using SPSS Statistics Version 20.0 (IBM). Continuous variables such as age, weight, and height were analyzed using Student's *t*-tests. Categorical data and SSI rate were assessed using the χ^2 test or Fisher exact test. Statistical significance was set at $P < 0.05$.

Results

A total of 172 participants were enrolled in this study. Among these, 16 participants were lost to follow-up and excluded from the analysis. The remaining 156 patients were equally allocated to the vancomycin and control groups (78 in each group). The mean age of the patients in the vancomycin and control groups were 59.3 years and 62.9 years, respectively. As presented in Table 1, the demographic characteristics of the two groups were statistically similar.

Surgical data

Fusion levels were defined as the number of intervertebral spaces from the upper instrumented vertebra to the lower instrumented vertebra[16]. The mean fusion levels were 2.65 ± 0.83 in the vancomycin group and 2.80 ± 1.62 in the control group. The mean blood loss was 250 ml (SD: 172.17) in the vancomycin group and 251 ml (SD: 113.07) in the control group. As present in Table 2, the two groups exhibited no differences in operative levels, mean blood loss, blood transfusion, operative duration, postoperative drain duration, or postoperative stay.

Primary outcomes

Vancomycin-related adverse reactions

During the 90-day follow-up period, no vancomycin-associated adverse reaction was observed. In particular, at the follow-up intervals of 2 weeks, 1 month, 2 months, and 3 months postdischarge, participants did not exhibit any instances of hypotension, hypersensitivity reactions, vancomycin-induced nephrotoxicity, osteoblast toxicity, or ototoxicity.

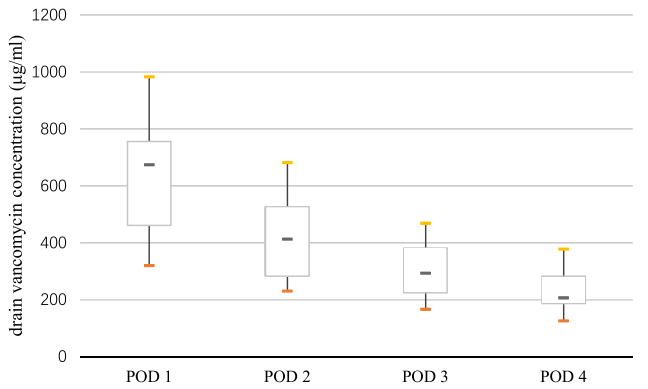

Figure 3. Postoperative drain vancomycin level. The mean drain vancomycin level reduced from POD 1 to POD 4 but was still higher than the minimum inhibitory concentration (15–20 μg/ml) of vancomycin. POD, postoperative day.

SSI

One patient in the vancomycin group developed a superficial SSI; bacterial isolation revealed *Pseudomonas aeruginosa* infection. No deep infection or space/organ infection cases were observed in the vancomycin group. Eight patients in the control group developed SSIs: seven patients developed superficial infections and one developed deep infection. No space/organ infection cases were observed in the control group. In the superficial infection cases of the control group, bacterial isolation revealed one case of *Escherichia coli* infection, one case of *Klebsiella spp.* infection, one case of *Streptococcus pneumoniae* infection, and two cases of *Staphylococcus aureus* infection; in two cases, the bacteria could not be identified. The deep infection case was identified to be *E. coli* infection (Table 3). All patients with SSIs improved after antibiotic therapy; surgical debridement was performed in cases with deep infection. The overall SSI rate was 5.8%. The SSI rate of the vancomycin group (1.3%) was significantly lower than that of the control group (10.3%), and the difference was statistically significant (RR = 0.125, 95% CI = 0.016–0.976).

Secondary outcomes

As presented in Table 4, the vancomycin group demonstrated significant decreases in WBC count (postoperative days [PODs] 3 and 5), neutrophil count (POD 3), ESR (POD 3), and CRP (POD 5) than the control group. As described in Figure 3, the average drain vancomycin concentration peaked on POD 1 and gradually decreased. However, the mean serum vancomycin concentration between PODs 1 and 5 was too low to be measured (< 0.24 μg/ml).

Discussion

Our study found that intrawound application of vancomycin can significantly reduce the SSI rate among patients who underwent posterior spine surgery without adverse effects. Intrawound application of vancomycin directly introduces the antibiotic to the wound at high concentrations for at least 4 days post-operatively, while systemic absorption of the antibiotic remains low.

In a multicenter study conducted at 20 hospitals in Washington, USA, more than half of the patients who underwent spine surgery received intrawound antibiotics[17]. Evidence from animal experiments indicates that the topical application of vancomycin can eliminate *S. aureus* contamination from surgical sites[18]. Several retrospective studies evaluating the use of intrawound vancomycin for spine deformities, cervical spine surgeries, and trauma found a significantly low SSI rate with local vancomycin use[19–21]. However, the effectiveness of topical vancomycin remains controversial, and the dosage of vancomycin powder varies widely in the literature. In our study, for patients in the vancomycin group, 1 g of vancomycin powder was applied over the muscle, fascia, and subcutaneous tissue before skin closure. This resulted in a significantly decreased SSI rate in the vancomycin group (1.3 vs. 10.3%). The drain vancomycin concentration was a median value of 674 μg/ml, which was > 30 times higher than the minimum inhibitory concentration of 15–20 μg/ml recommended by the Infectious Diseases Society of America[22]. Notably, vancomycin is a time-dependent antibiotic, and its microbicidal activity does not change with increasing concentration[23]. Further research is required to refine the dosage of vancomycin powder according to influencing factors, such as the length of fusion levels.

In the 90-day follow-up period, no vancomycin-associated adverse reaction was reported. Historically, vancomycin-related adverse reactions have been associated with the impurities that may be present[24,25]. Improvements in the manufacturing process have greatly reduced this toxicity. A few studies have reported severe adverse outcomes in patients who received local treatment with vancomycin. Nagahama *et al.*[26] described a patient who was administered intrawound vancomycin to treat Redman syndrome and recovered without sequelae after symptomatic treatment. In another case report, seven patients who underwent spinal surgery developed severe hypotension after local application of vancomycin[27]. However, the report did not provide any laboratory results. To our knowledge, there are no large-scale retrospective studies on the complications associated with topical application of vancomycin.

Intrawound application of vancomycin decreases the SSI rate while minimizing the incidence of vancomycin-associated adverse effects. Nephrotoxicity is the most common adverse effect of intravenous vancomycin and reportedly occurs in up to 20% of patients after conventional doses of vancomycin therapy[28]. Although the mechanism of vancomycin-related nephrotoxicity remains elusive, oxidative stress on the renal proximal convoluted tubule is hypothesized to be a potential mechanism[29]. Moreover, several animal studies have demonstrated that the use of antioxidants is beneficial in preventing vancomycin-induced nephrotoxicity[30,31]. In the majority of studies, nephrotoxicity is defined as a 0.5 mg/dl elevation in serum creatinine if the initial serum creatinine was ≤ 3 mg/dl or an increase of > 1 mg/dl if the initial serum creatinine was > 3 mg/dl[25]. In our study, we measured the creatinine and urea nitrogen levels in both groups but found no significant differences.

Adverse reactions such as osteoblast toxicity, hypotension, and ototoxicity occur at relatively lower frequencies. Concerning the potential osteoblast toxicity associated with vancomycin, Guimbard-Pérez *et al.*[32] indicated a 32% reduction in fusion rates within the vancomycin-treated group compared to controls following the application of a dose five times the standard in a rabbit spine model. Additionally, an *in vitro* study demonstrated

that a concentration of 7500 mg/ml of vancomycin was cytotoxic to osteoblasts[33]. In contrast, our study, wherein 1 g of vancomycin powder was directly to the surgical wound, showed that the peak concentration of vancomycin in the drainage fluid on the POD 1 was 983 μg/ml, which is significantly lower than those in the aforementioned *in vitro* research.

Only a few studies have evaluated the pharmacokinetics of the intrawound application of vancomycin, and most of the previous studies were based on intravenous infusion models. Armaghani *et al*.[34] and Sweet *et al*.[35] assessed the local use of vancomycin in spinal surgery and found that it could provide high local dose concentrations while avoiding high systemic concentration, which is consistent with our study's findings. However, the pharmacokinetics of topical vancomycin may vary depending on the surgical site[36]. Therefore, these findings should be interpreted with caution.

Limitations

Our study has several limitations. First, in this study, vancomycin was applied to deep soft tissues of the incision, such as the muscle, fascia, and subcutaneous tissue. However, during the follow-up, we observed that the reduction in SSIs pertained specifically to superficial infections. Second, in the present study, the causative organisms isolated included *E. coli* and *Klebsiella spp*.. These bacteria are gram-negative, and vancomycin exhibits no antimicrobial activity against them. Consequently, the observed reduction in the rate of SSIs caused by Enterobacteriaceae cannot be attributed to a benefit of vancomycin use. Additionally, this investigation was limited by its 90-day follow-up duration, which is insufficient for observing long-term complications, such as the rates of bone graft fusion. Moreover, the relatively low incidence of SSIs among participants within this study limits the thoroughly assessment of the impact of topical vancomycin on postoperative microbiota. Lastly, the study did not explore postoperative functional outcomes using established measures such as the Oswestry Disability Index or the Visual Analog Scale for outcome assessment.

Conclusions

The intrawound application of vancomycin powder is a safe and effective method for reducing the risk of SSIs among patients undergoing PLIF surgery. Intrawound application of vancomycin powder delivers a high concentration of the antibiotic directly to the surgical site. No vancomycin-associated adverse effect occurred during follow-up.

Ethical approval

This study was approved by the Institutional Review Board of Beijing Chaoyang Hospital (2022-1-18-3), and the protocol was registered in the Chinese Clinical Trial Registry (ChiCTR2200058050). All patients were informed about the study design and agreed to participate.

Consent

This was a prospective, double-blind, randomized controlled study involving patients who underwent PLIF surgery and received intrawound vancomycin powder treatment. This study was approved by the Institutional Review Board of Beijing Chaoyang Hospital (2022-1-18-3), and the protocol was registered in the Chinese Clinical Trial Registry (ChiCTR2200058050). All patients were informed about the study design and agreed to participate. No patients' names, initials, or hospital numbers were directly shown in the paper.

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Author contribution

H.B., L.-H.Y., and P.-A.X.: concept and data collection; G.L., C.-F.Q., and Z.-M.Z.: literature review; H.B., L.-H.Y., and C.-S.L.: statistical data analysis and interpretation; L.-H.Y. and H.B.: article drafting; L.-Y.Z., P.-A.X., and Y.H.: critical revisions of the article. All the authors have read and approved the manuscript.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

The protocol was registered in the Chinese Clinical Trial Registry (ChiCTR2200058050).

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Data availability statement

Information used to access the data in this study is included in this article. If necessary, the corresponding author can be contacted to obtain more data.

Provenance and peer review

Not applicable.

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