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ORIGINAL RESEARCH

Does the Microflora of Surgery Site Infection Change After Prophylactic Use of Vancomycin Powder in the Spine Surgery

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Study Design: Retrospective cohort study.

Objective: This study aimed to investigate the characteristics of microflora in patients with deep spinal surgical site infection (SSI) after prophylactic use of vancomycin powder (VP).

Methods: A retrospective analysis was performed on patients after spinal surgery. Patients were grouped according to whether VP use and only patients with deep SSI were included in this study. General information of the patients, the dose of vancomycin, bacterial culture results, drug sensitivity test results, and SSI treatment methods were recorded. The differences of microflora between the two groups were analyzed, and the sensitivity of bacteria in the +VP group to antibiotics was analyzed.

Results: The infection rate in the +VP group was 4.9% (56/1124) vs 6.3% (93/1476) in the No-VP group ($P < 0.05$). The proportion of Gram-positive bacteria (GPB) in the +VP SSIs was 55.4% vs.74.1% in the No-VP group ($P < 0.05$). The percentage of Gram-negative bacteria (GNB) in the +VP SSIs was 46.4% vs.30.1% in the No-VP group ($P < 0.05$). More dose of VP cannot decrease the SSI, but the proportion of GNB in VP >1g SSIs was higher (59.0% vs 32.4%, $P < 0.05$). In the +VP SSIs, all of the GNB cultured were sensitive to meropenem, and linezolid covered most of the GPB cultured.

Conclusion: Local use of vancomycin powder can reduce the incidence of SSI, but this may lead to changes in the bacterial flora. Once the SSI occurs, the case of GNB infection may be increased. The more dose of VP cannot decrease SSI but may increase the rate of GNB in the +VP SSIs. Once infections still occur after VP use, antibiotics covering GNB may be added. These findings may help guide choice of empiric antibiotics while awaiting culture data.

Keywords: surgery site infection, microflora, spine, vancomycin

Introduction

Surgical site infection (SSI) is a serious complication of spinal surgery, which can lead to failure of internal fixation, spinal instability, neurological dysfunction, sepsis, death, and increased medical costs.[1–3] Vancomycin is a glycopeptide antibiotic that acts mainly by destroying the cell walls of sensitive bacteria. Topical use of vancomycin powder in spinal surgery not only creates a higher drug concentration at the surgical site but also reduces drug diffusion in blood, so it has the dual advantages of improving antimicrobial efficiency and reducing the side effects.[3] Many studies have shown that prophylactic use of vancomycin powder can effectively reduce the incidence of SSI.[1,4–7]

However, SSI still occurs after prophylactic use of vancomycin. Many studies reported that the SSI rate after VP use is 0.9–3.1%, which shows that VP dose did not completely eliminate SSI.[4,5,7] Previous studies have shown that GPB are

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the main pathogenic bacteria, followed by GNB and anaerobes in SSIs,[8] but all the studies of microflora were based on patients without VP use. Whether vancomycin alters the microflora of SSIs remains unknown.

Antibiotics are the mainstay treatment for deep site infections after spinal surgery. It is important to know the type of infection, and broad-spectrum antibiotics should be administered as soon as possible when SSI occurs.[9,10] Whether the use of vancomycin powder causes changes in bacterioflora is still unknown, this will affect the treatment strategy for the secondary infection. Therefore, we retrospectively analyzed SSIs after topical use of VP. The change of microflora and treatment strategy of the secondary infections were analyzed, aiming to help guide the choice of empiric antibiotics while awaiting culture data and improve the antimicrobial prophylaxis strategies for SSI after topical use of VP.

Method

A retrospective analysis was performed on patients who underwent spinal surgery in our institution between January 2015 and December 2020. Patients with intraoperative local use of VP were included in the +VP group, and those without were included in the No-VP group. The patient consent to review their medical records was waived due to the retrospective nature of this study by the Institutional Review Board and the Ethics Committee of Henan Provincial People's Hospital. We pledge to respect the privacy of all participants, and all data involved in this study were anonymous and kept in a confidential manner. The study was based on the Declaration of Helsinki, as revised in 1983.

Diagnostic Criteria for SSI

Only deep SSIs were included in this study. The diagnosis of SSI was based on standards set by the Center for Disease Control and Prevention.[11] Which is at least one of the following conditions must be met: (1) abscess formation or outflow of pus from the deep site; (2) accompanied by fever (over 38°C), local pain, or tenderness; (3) intraoperative diagnosis or postoperative histopathological confirmation of debridement; (4) abscess at the depth of the surgery site demonstrated by imaging examination; (5) deep SSI diagnosed by the surgeon.

Inclusion Criteria

The inclusion criteria were as follows: (1) patients underwent spinal surgery, degenerative diseases, fractures, deformities, or tumors are all included; (2) complete treatment record which included whether vancomycin was prophylactic used intraoperatively, the dose of vancomycin and specific treatment methods when SSI occurred; (3) only primary surgery was included in this study.

Exclusion Criteria

The exclusion criteria were as follows: (1) superficial SSI; (2) spinal infections such as tuberculosis and fungal infections; (3) patients with immunodeficiency or taking immunosuppressive drugs; (3) allergy to cephalosporin antibiotics or vancomycin; (4) incomplete medical records; (5) non-acute infection cases which means SSI occurred over 3 months postoperatively.[12]

Prophylactic Antibiotic Use Protocol

All patients receive pre-operative washes with chlorhexidine. A routine prophylactic use of antibiotics was applied in both groups, including intravenous application of 1.5g cefuroxime 1 h before surgery, an additional group every 4h during surgery, and 1.5g Q8h within 24h after surgery. In the +VP group, VP was sprayed into the wound during the operation, and the powder was evenly distributed in the sub-fascia and outer fascia according to the types of the surgery and the judgment of the surgeon.

Observational Index

Demographic characteristics of the patients, the dose of topical vancomycin, the type of postoperative infection, bacterial culture results, drug sensitivity test results, and the treatment of SSI were recorded. The bacterial culture specimen included blood, wound secretions and specimen obtained during the surgery. The culture methods mainly included smear

identification of common bacteria and fungi, culture, drug sensitivity tests and drug sensitivity tests of anaerobic and aerobic bacteria.

Statistical Analysis

SPSS17.0 statistical software was used for the analysis. Quantitative data are expressed as mean ± standard deviation (x ± s). *t*-test of independent samples was used for comparison between the VP and the No-VP groups. The qualitative data were compared by chi-square test. Multiple comparisons were performed using Bonferroni's method on the basis of chi-square test. $P < 0.05$ were considered statistically significant.

Results

Local vancomycin powder was used in 1124 patients, SSI occurred in 56 patients, and the infection rate was 4.9%. A total of 1476 patients were included in the No-VP group, and 93 patients developed SSI, the infection rate was 6.3%. There was a significant difference in infection rates between the two groups ($P < 0.05$). There were 56 patients in the +VP group, including 24 males and 32 females, with an average age of 56.7 ± 14.2 years. Vancomycin powder was used during the operation, with an average dose of 1.7 ± 0.8g. There were 1476 patients in the No-VP group, 93 patients developed SSIs including 57 males and 36 females, with an average age of 64.9±10.3 years. We included date from fracture, degenerative disease, scoliosis and tumor cases, and there was no significant difference in the distribution of disease types between the two groups ($P > 0.05$). In the VP group, there were 1008 instrumented cases and 106 no-instrumented cases. In the No-VP group, there were 1334 instrumented cases and 142 no-instrumented cases. There was no significant difference in the two groups (Table 1).

In the +VP SSIs, there were 5 cases (8.1%) of cervical spine infection, 13 cases (23.2%) of thoracic spine infection, and 38 cases (67.9%) of lumbar spine infection. In the No-VP group, there were 12 (12.9%) cervical vertebra infections, 19 (20.4%) thoracic vertebrae infections, and 62 (66.7%) lumbar vertebrae infections. There was no statistical difference in the distribution of infection sites between the two groups ($P > 0.05$) (Table 1).

In the +VP group, the positive detection rate of bacteria was 80.4% (45/56) and 11 patients were cultured negative, which was diagnosed by the clinical diagnostic criteria. In the No-VP group, the positive detection rate of bacteria was 79.6% (74/93) and 19 patients were cultured negative. In the +VP group, 31 cases of GPB, 2.8% (31/1124) in total patients, 26 cases of GNB, 2.3% (26/1124) in total patients, 3 cases of fungi, and 8 cases of mixed infection with multiple bacteria were cultured. In the No-VP group, 69 cases of GPB, 4.7% (69/1476) in total patients, 28 cases of GNB, 1.9%

Table 1 General Conditions of Patients and Distribution of Infected Sites in 2 Groups

	+VP	No-VP	P value
Age (years)	56.7±14.2	64.9±10.3	0.147
Gender (male/female)	24/32	57/36	0.324
Dose of VP (g)	1.7±0.8		
Total rate of infection	4.9%	6.3%	0.032
Total rate of G+ bacteria infection	2.8%	4.7%	0.041
Total rate of G- bacteria infection	2.3%	1.9%	0.176
Disease types			0.112
Fracture	324	591	
Degenerative disease	676	826	
Scoliosis	76	97	
Tumor	48	62	
Instrumented/No-instrumented	1008/116	1334/142	0.554
Infection site			0.421
Cervical	5 (8.1%)	12 (12.9%)	
Thoracic	13 (23.2%)	19 (20.4%)	
Lumbar	38 (67.9%)	62 (66.7)	

Table 2 Bacterial Culture Results of Wound Infections in 2 Groups

Organism	+VP (n = 56)	No-VP (n = 93)	P-value
Gram-positive organism	31 (55.4%)	69 (74.1%)	0.013
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	13	27	
Streptococcus	4	12	
Coagulase-negative *Staphylococcus* (CNS)	2	8	
Methicillin-resistant *Staphylococcus aureus* (MRSA)	12	22	
Gram-negative organism	26 (46.4%)	28 (30.1%)	0.012
Escherichia coli	9	16	
Pseudomonas aeruginosa (PA)	2	1	
Proteus	1	None	
Klebsiella	4	3	
Enterobacter	6	7	
Serratia marcescens	2	None	
Corynebacteria	2	1	
Fungus	3(5.4%)	1(1.0%)	0.032
Candida albicans	2	1	
Aspergillus	1	None	
Culture negative	11	19	
Polymicrobial organism	8 (14.3%)	10 (10.8%)	0.031

(28/1476) in total patients, 1 case of fungus, and 10 cases of mixed bacterial infection were cultured, and the proportion of Gram-positive bacteria was 55.4% and 63.4% in the 2 groups ($P < 0.05$). Among all cases, the total rate of GPB infection is 2.8% in the +VP group and 4.7% in the No-VP group ($P < 0.05$), meanwhile the rate of GNB is 2.3% in the +VP group and 1.9% in the No-VP group ($P > 0.05$) (Table 2 and Figure 1).

When subgroup analysis was performed on SSI cases, the proportion of GPB in the +VP SSIs was 55.4% vs.74.1% in the No-VP group ($P < 0.05$). The GNB rate in the +VP SSIs was 46.4% and 30.1% in the No-VP ($P < 0.05$). The fungal proportion in the +VP SSIs was significantly higher than that in the No-VP group (5.4% vs.1.0%) ($P < 0.05$) (Table 2).

The sensitivity test results of GPB and GNB cultured in the +VP group were analyzed. The GNB cultured showed higher sensitivity to cefixime, ceftazidime and ceftriaxone, reaching 60% to 95%, and all of the cultured bacteria were sensitive to meropenem. The sensitivity of GPB cultured to vancomycin, teicoplanin and macrodantin as 80% to 90%, and linezolid has the highest sensitivity (Table 3).

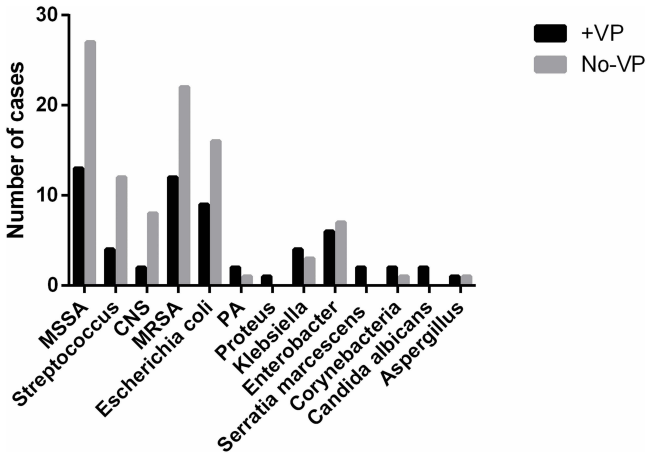

Figure 1 The bacteria cultured in the +VP and No-VP group.
Abbreviations: VP, vancomycin powder; MSSA, methicillin-sensitive*Staphylococcus aureus*; CNS, coagulase-negative*Staphylococcus*; MRSA, methicillin-resistant*Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*.

Table 3 Drug Sensitivity Test Results of Bacteria Cultured in the +VP Group

Bacterial Species	Antibiotics	Sensitivity (%)
Gram-negative organism	Amoxicillin Penicillin Erythromycin Gentamicin Ampicillin	<10
	Benzylpenicillin Piperacillin Cefoperazone	10–50
	Cefixime Ceftazidime Ceftriaxone	60–95
	Meropenem	100
Gram-positive organism	Aminoglycosides Macrolides Sulfonamides	<10
	Cefixime Ceftazidime Ceftriaxone	10–50
	Vancomycin Teicoplanin Macrodantin	80–90
	Linezolid	>90

Of the +VP SSIs, the treatment methods were analyzed, and the days between the debridement and first procedure were 13.4 ± 7.1 days. And 15 cases of fracture, 30 cases of degenerative disease, 6 cases of scoliosis and 5 cases of tumor were included. Among which including 6 cases of debridement, 32 cases of debridement and closed irrigation, 18 cases of debridement and vacuum sealing drainage (VSD). Whether a vacuum device was applied depends on the size of the wound, this was decided by the surgeon. The average number of procedures was 3.7 ± 2.1. Multiple comparisons were performed on the infection rate of different disease, and no significant difference was found ($P > 0.05$). But the infection rate in the scoliosis (7.7%) and tumor (10.2%) is higher than that in fracture (4.7%) and degenerative disease (4.4%) (Table 4).

Subgroup analysis was performed on VP dose, and patients were divided into VP ≤1g and VP >1g group. The amount of VP used in the two groups was 0.8 ± 0.4 and 1.6 ± 0.7g, respectively. There was no significant difference in the total infection rate between the two groups ($P > 0.05$), and no significant difference in the GPB infection in VP ≤1g and VP >1g SSIs and fungal infection in VP ≤1g and VP >1g SSIs ($P > 0.05$), but the proportion of GNB in VP >1g SSIs was higher than that in VP ≤1g SSIs (59.0% vs 32.4%, $P < 0.05$) (Table 5 and Figure 2).

Table 4 Clinical Characteristics and Treatment Methods in the +VP SSIs

Days Between the Debridement and First Procedure	13.4 ± 7.1
Disease types (n = 56)	
Fracture	15
Degenerative disease	30
Scoliosis	6
Tumor	5
Surgery method	
Debridement	6
Debridement and irrigation	32
Debridement and vacuum sealing drainage	18
Number of procedures	3.7±2.1

Table 5 Distribution of Infected Rate in VP ≤1g and VP >1g Groups

	VP ≤1g	VP >1g	P value
Total rate of infection	5.4% (34/625)	4.4% (22/499)	0.491
Dose of VP (g)	0.8±0.4	1.6±0.7	
GNB infection in SSIs	32.4% (11/34)	59.0% (13/22)	0.045
GPB infection in SSIs	61.8% (21/34)	45.5% (10/22)	0.278
Fungus infection in SSIs	5.9% (2/34)	4.5% (1/22)	0.661

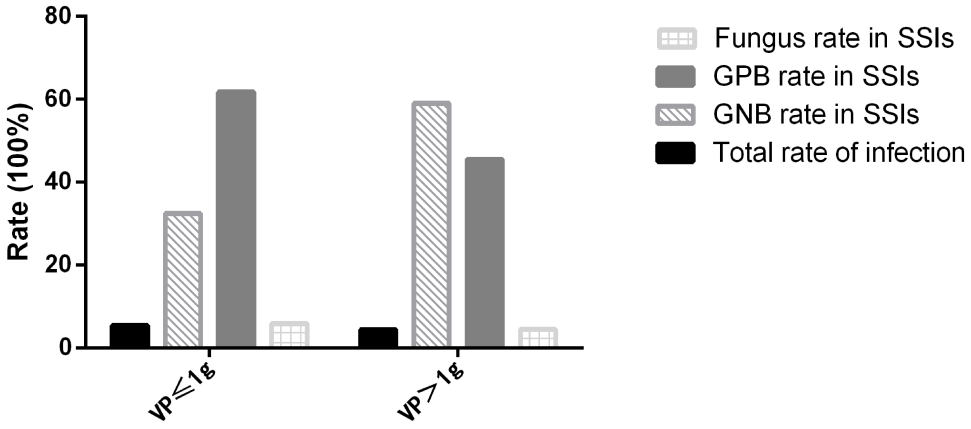

Figure 2 The bacterial flora distribution between the VP≤1g and VP>1g SSIs.
Abbreviations: VP, vancomycin powder; GPB, gram-positive bacteria; GNB, gram-negative bacteria.

Discussion

Vancomycin reduces infection by increasing the local concentration of the drug and reducing the chance of bacterial biofilm production. Hovis et al[2] created a rabbit surgical model with fixation of implants at a tibial surgical site seeded with MRSA. They found that VP could decrease the risk of infection and biofilm formation on the implants, and the vancomycin levels in serum were minimally increased at the same time. A total of 2600 patients were enrolled in this study, and postoperative infections were analyzed. Local use of vancomycin powder can reduce the incidence of SSI, but this may lead to changes in the bacterial flora. The case of GNB infection may be increased in the secondary SSIs. The more dose of VP cannot decrease SSI but may increase the rate of GNB in the +VP SSIs at the same time.

Many studies came to a conclusion that topical use of VP can effectively reduce SSI.[4,5,13] Dodson et al[4] conducted a systematic review and found that VP significantly reduced the relative risk of SSI (RR = 0.55, $P < 0.0001$). In this study, compared to the No-VP group, the SSI in the +VP group decreased from 6.3% to 4.9%. In the previous study, the SSI rate is 0.9–3.1%, the SSI rate in the +VP group in this study is higher than previous date, this may be due to the inclusion of scoliosis and tumor cases.

Many previous studies focused on the change of infections caused by *Staphylococcus aureus* after vancomycin use.[1,14] In this study, we also found a decrease in *Staphylococcus* infections, which is 1.1% (13/1124) in the +VP group and 1.8% (27/1476) in the control. Besides, by analyzing the bacterial flora distribution, we found that the overall infection rate was reduced by reducing the rate of GPB infection (2.8% vs 4.7%, $P < 0.05$), while the rate of GNB infection did not change (2.3% vs 1.9%, $P > 0.05$), which means that the most important reason for the decrease of SSI is the decrease of GPB infections after topical use of VP.

Vancomycin is a glycopeptide antibiotic widely used for the treatment of infections caused by GPB but is inefficient against GNB.[15] The cellular integrity and morphology of most GNB are maintained by peptidoglycan, which consists of glycan strands cross-linked by peptides, whose arrangement determines cell shape and prevents lysis due to turgor pressure.[16] Vancomycin is inherently inactive toward GNB because of its inability to cross the outer membrane.[17] However, the GNB rate of total patients was equal in the groups. But of the SSI cases, the GNB rate in the +VP group was 46.4% and 30.1% in the No-VP group ($P < 0.05$). Many studies conducted the same conclusion. Ghobrial et al[18] compared the causative pathogens among the patients who developed SSI. They found that 31 of 51 (60.7%) vancomycin-treated SSI patients were positive for GNB, while only 12 of 57 patients were found to be positive for GNB in the control. Adogwa et al[7] demonstrated that over half of the secondary SSIs after VP use were positive for GNB.

Since the rate of GPB infection decreases, the percentage of SSI caused by GNB would increase. At the same time, the flora disequilibrium may increase opportunistic infections. The changes in commensal communities alter the interaction between pathogens, enhancing not only the production of certain T cell subsets but also altering the cytokine expression in immune innate and adaptive cells.[19] Scheithauer et al[20] conducted that short-term vancomycin treatment

increases the abundance of Gram-negative opportunistic pathogens and immunogenic bacterial components. Rosa et al[19] indicate that the bacterial community found in vancomycin-induced dysbiosis increased opportunistic infections.

The effect of VP dose on SSI subgroup was analyzed. We found that VP dose did not affect the incidence of SSI, nor did it affect the rate of GPB and fungi in the SSI cases, but the GNB infection rate in SSI cases increased in the VP >1g group (59.0% vs 32.4%), which was consistent with the higher GNB infection rate in the +VP SSIs. Dodson et al[4] conducted a systematic review, and they demonstrated that the more dose of VP cannot significantly reduce SSI but may inhibit bone remodeling. What is impressive is that the rate of GNB SSI in the VP >1g SSIs is higher than that in the VP ≤1g (59.0% vs 32.4%); this also confirms that vancomycin inhibits the growth of GPB, and the flora disequilibrium may increase opportunistic infections.

Linezolid is an anti-infective drug with GPB SSI after VP use. According to the experimental results, the sensitivity to linezolid was over 90%. Many previous studies have confirmed that linezolid is superior to vancomycin.[15,21–24] Fernandes et al[15] compared the efficacy of linezolid and vancomycin on MRSA burden and found that treatment with linezolid has a greater beneficial effect. Moreover, linezolid was found to be more effective in patients complicated with underlying diseases. Among diabetic patients with MRSA infection, linezolid is clinically more effective than vancomycin.[25] The authors found that all of the GNB SSIs were sensitized to meropenem. Carbapenems have a wider antimicrobial spectrum and lower sensitization. Samuel et al[26] studied the bioactivity of meropenem and meropenem was biologically active against S. aureus, P. aeruginosa, E. coli, and K. pneumoniae. In the treatment of polymicrobial SSIs, meropenem was found to be the most effective single agent (90–95%), and its efficacy was even improved by adding vancomycin (97–98%).[27,28]

It was also worth noting that the higher rate of GNB infections in the +VP SSIs, which means in high-risk patients antibiotics covering GNB should be considered in primary surgery. This will help reduce the incidence of SSI, either GPB infection or GNB infection. Salimi[26] and Gande[29] hold the same opinion, they conducted that the strategy of vancomycin use needs to be individualized and antibiotic use strategies for GNB need to be improved.

At the same time, our study has limitations. Firstly, this was a single-center retrospective study, the flora in different regions and different seasons have different manifestations and nasal swabs for bacterial culture did not apply before surgery which may influence the research results.[30,31] Secondly, the effect of vancomycin can be influenced by many uncontrollable factors, although the two groups showed no difference in patient age, sex, and diagnosis, but the ambulatory status, bowel/bladder incontinence, chronic respiratory insufficiency nutritional issues which are confounding factors influencing experimental results.[32,33] Finally, although the effect of vancomycin dosage on postoperative SSI was initially discussed in this paper, the method of surgery, operation timing, and the fixed segments would affect the results.[34,35]

Conclusion

Local use of vancomycin powder can reduce the incidence of SSI, but this may lead to changes in the bacterial flora. Once the SSI occurs, the cases of GNB infection may be increased. The more dose of VP cannot decrease SSI but may increase the rate of GNB in the +VP SSIs. Once infections still occur after topical use of VP, antibiotics covering GNB may be added. These findings may help guide the choice of empiric antibiotics while awaiting culture data.

Data Sharing Statement

All of the data are described in the manuscript. The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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