# Use of intrawound vancomycin powder against postoperative infection after spine surgery

Hiroshi Takahashi, Yasuaki Iida, Yuichirou Yokoyama, Keiji Hasegawa, Shintaro Tsuge, Katsunori Fukutake, Kazumasa Nakamura and Akihito Wada

*Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan*

**Abstract:**

Local application of vancomycin has recently become widely used in spine surgery. However, local application is not included in the indication and has not been approved by the US Food and Drug Administration (FDA). Thus, we searched for reports with "intra wound-vancomycin" and "SSI" as keywords in the MEDLINE database, and investigated the efficacy, problems with use, and future prospects based on these reports. Intrawound vancomycin was described as effective in most of the reports, but was found to have no effect or to aggravate the condition in some reports. A toxic effect on osteoblasts due to a high local concentration was described in some reports, whereas local application was found to be safe in other studies. The amount of vancomycin used and the administration method varied among the reports. Overall, the results suggest that intrawound vancomycin is clinically effective, but this has yet to be established in a randomized controlled trial. There is a need to identify cases that should be selected for this treatment and to investigate the dose and optimum concentration of vancomycin for clinical use.

**Keywords:**

Spine surgery, Surgical site infection, Intrawound vancomycin, Antimicrobial prophylaxis

Spine Surg Relat Res 2018; 2(1): 18-22

dx.doi.org/10.22603/ssrr.2016-0002

## Introduction

Surgical site infection (SSI) after spine surgery is a serious complication, but many patient and environmental factors are involved in SSI and complete avoidance is difficult. Thus, SSI has occurred at a consistent rate in previous studies, despite various countermeasures being taken[1-14]. Once infection occurs, further surgery and long-term antimicrobial drug administration are necessary to control infection in many cases, resulting in prolongation of hospital stay and an increased cost of medical care[15-19]. Infection may ultimately be remitted, but SSI reduces the degree of satisfaction and functional prognosis of the patient after surgery[20-23].

Antimicrobial prophylaxis (AMP) is useful to prevent infection after spine surgery. Guidelines in many countries[24-26] specify cefazolin (CEZ) for targeting *Staphylococcus aureus*. However, difficult SSI cases with methicillin-resistant *Staphylococcus aureus* (MRSA) as a causative agent have recently increased[18,27-29], and vancomycin (VCM) has been used for AMP, with the aim of reducing MRSA infection. Routine use of VCM to prevent infection is not recommended, and local application is off-label and not described in the package insert. However, the usefulness of local application of VCM has been widely described[14,19,30-32], although often in observational studies, which suggests that these results should be carefully interpreted. Moreover, aggravation of infection[33] and no effect[34] have been described for VCM in some studies. In the only randomized controlled trial (RCT), the incidence of SSI did not change in cases treated with intrawound VCM[35].

Therefore, local VCM is not approved by the US Food and Drug Administration (FDA), and guidelines established by the Japan Society of Chemotherapy and Japan Society for Surgical Infection handle this as an unresolved issue because of the unclear efficacy and safety[26]. In this report, we examine the benefits and concerns of use of intrawound VCM.

Corresponding author: Hiroshi Takahashi, drkan@med.toho-u.ac.jp

Received: September 30, 2016, Accepted: February 21, 2017

## Methods

A MEDLINE search for pertinent literature was conducted using the following MeSH search terms: "intrawound vancomycin" and "SSI." High-quality reports were selected and further literature was evaluated from references in these reports. The utility, safety, problems, and future prospects of intrawound VCM are discussed based on the contents of the reports.

## Results and Discussion

SSI-causative bacteria are most frequently *Staphylococcus aureus*, and especially methicillin-susceptible *Staphylococcus aureus*, but the frequency of MRSA has also been increasing. In the USA and UK, about 50% of bacteria detected in infected patients in intensive care units are MRSA[18,27-29]; i.e., the AMP protocol currently administered intravenously is effective for only about 50% of hospital infection cases. Thus, intrawound vancomycin has recently been clinically applied and its efficacy has been frequently reported[14,19,30-32], but the effect has also been questioned in some reports[33,34]. Therefore, we investigated the efficacy and problems from various perspectives.

### *1. Incidence of SSI after spine surgery*

In Japan, the incidence of SSI was 3.73% in all spinal instrumentation surgeries performed at 2,241 training facilities certified by the Japanese Orthopaedic Association-[2] and 1.1% in a survey of 31,380 patients reported by the Japanese Society for Spinal Surgery and Related Research[3]. The incidences of SSI in studies limited to instrumented spine surgery have ranged from 0.4 to 15%[4-14]. As a matter of course, the incidence of SSI rises when the operative time is prolonged in instrumented surgery, and in trauma cases compared with cases treated with decompression alone.

### *2. Medical costs and cost of VCM for SSI*

The 500,000 cases of SSI that occur each year account for up to US$10 billion in US health care expenditures[15]. Calderone et al. estimated that health care costs can increase up to fourfold once an infection occurs after spinal surgery[16]. Godil et al. showed that the cost of care for one deep spine infection case is over US$33,000[17]. The cost of a 1 g dose of VCM is US$10-44[14,17-19], with this cost varying depending on the type of insurance.

### *3. Functional prognosis after SSI*

Weinstein et al.[20] found that SSI occurred after spine surgery in 46 (1.9%) of 2,391 patients over a 9-year period, flap preparation was necessary to close the wound in 3 cases, and pseudoarthrosis was formed in 3. Collins et al.[21] reported postoperative infection in 74 of 1,980 patients treated with instrumented surgery between 1993 and 2003. Excluding 39 cases with insufficient description of the postoperative course, the lesions were pain free and the spines were stable in 16 (46%) of 35 cases, but complaints such as low back pain remained in the other cases. In a propensity score-matched case-control study, in which SSI occurred in 30 of 1,144 patients treated with instrumented lumbar spinal fusion between 2001 and 2008, Petilon et al.[22] found significantly poorer improvement of low back pain at 2 years after surgery in patients with SSI. Chen et al.[23] evaluated clinical symptoms and daily activity level at 2 years after surgery in 51 patients with postoperative spinal implant infection after instrumented surgery between 1997 and 2007. Of 47 survivors, low back pain aggravated in 10 (21.3%), daily activity did not change in 17 (36.2%) and aggravated in 12 (25.5%), and 7 (14.9%) became wheelchair-bound or bedridden. These reports show that even with control of SSI, complaints such as low back pain persist at a high rate and interfere with daily activities.

### *4. Effectiveness of intrawound VCM*

In a study of 253 cases of lumbar spine surgery performed by the same surgeon at the same facility, Strom et al.[14] found an incidence of SSI of 0% in 97 cases treated with 1 g of intrawound VCM compared with 11% in 156 cases that were not treated with intrawound VCM. The incidence of SSI decreased from 12 to 0% in instrumented cases, and from 10 to 0% in non-instrumented cases. In 1,778 cases of thoracic and lumbar instrumented spinal fusion performed by three surgeons, Sweet et al.[19] found incidence of SSI of 0.2 and 2.6% in patients treated with 2 g of intrawound VCM (n=911) and without VCM (n=821), respectively, with a significant decrease in the incidence produced by VCM application.

In a study of application of 1 g of intrawound VCM in 1,512 spine surgeries, Molinari et al.[30] found deep SSIs (only deep SSIs were investigated because the definition of superficial SSIs was considered to be ambiguous) in 15 cases (0.99%), including 8 of 663 instrumented spinal surgeries (1.20%) and 7 of 849 uninstrumented surgeries (0.82%). In particular, the incidence of SSI was 1.23% (4/324) in multilevel instrumented posterior spinal fusion, 0.55% (1/183) in trauma cases, and 1.15% (1/87) in revision surgeries. The incidence was lower than that found in previous reports, which suggested that intrawound VCM is effective. However, the absence of a control group is an important limitation of this study.

Ghobrial et al.[31] reviewed 16 reports including 9,721 cases, of which VCM was used in 6,701 (68.9%) and SSI developed in 1.36 and 7.47% of cases with and without VCM treatment, respectively. However, although intrawound VCM appeared to reduce the incidence of complications, it was pointed out that the FDA has not approved this treatment because none of the reports described a well-designed prospective study. Gaviola et al.[32] reported the results of application of 2 g of intrawound VCM in 326 cases of instrumented multilevel spinal fusion. The incidence of SSI was 5.2 and 11.0% with and without VCM application, respectively, and the treatment was concluded to be useful based

on the results of multivariate analysis.

### *5. Local and blood concentrations of intrawound VCM*

Local application of VCM has many reported benefits[14,19,30-32]. A characteristic of local VCM application is a low serum VCM level because of low local absorption, despite the local level being significantly higher than the minimal inhibitory concentration (MIC) for bacteria covered by VCM in surgical wounds. Clinical studies show that serum VCM remains at normal therapeutic levels (15-20 μg/mL) or subtherapeutic to undetectable levels[36]. Sweet et al.[19] applied 2 g of VCM to the local site when the wound was closed, and simultaneously measured VCM in surgical drainage and serum on postoperative days (PODs) 0, 1, 2, and 3 in 178 patients. In surgical drainage, VCM was detected at 1,457, 462, 271, and 128 μg/mL on PODs 0, 1, 2, and 3, respectively, but the VCM level in blood collected simultaneously was lower than the detection limit (0.6 μg/mL) in 80% of the patients, and the mean level on POD 1 was 1.6 μg/mL in the 20% of cases in which VCM was detectable. The level detected in wounds was about 1,000 times the MIC of MRSA and coagulase-negative *Staphylococcus*. The risk of emergence of resistant bacteria was concluded to be low due to poor absorption of VCM into the blood, and complications caused by systemic administration, such as renal disorder and hearing impairment, did not occur.

### *6. Complications of intrawound VCM*

Routine use of VCM for AMP may cause SSI with Gram-negative bacteria and anaerobes and promote emergence of VCM-resistant organisms[31,37]. Adverse effects of systemic administration of VCM include renal toxicity, ototoxicity, and Red man syndrome.

Cytotoxicity in local application of VCM powder is of concern because of the potential influence of a high concentration of VCM on osteoblasts. Edin et al.[39] investigated the influence of CEZ and VCM on osteoblasts cultured in the presence of 0, 10, 100, 1,000, and 10,000 μg/mL of the antibiotics. VCM showed no influence up to 1,000 μg/mL and was toxic at 10,000 μg/mL. CEZ showed no influence up to 100 μg/mL, but was toxic at 200 μg/mL in repeated tests. Thus, it was concluded that VCM is safer than CEZ at the high concentration required for a local spray. Eder et al.[40] collected osteoblasts from bone tissue in 10 patients and investigated osteoblast migration, proliferation, and viability and the pH in solutions of 0, 3, 6 and 12 mg/cm$^2$ VCM. The pH significantly decreased at ≤3 mg/cm$^2$, the migration potential of osteoblasts decreased in a dose-dependent manner and was 0% at 12 mg/cm$^2$, cell proliferation was significantly inhibited at ≥3 mg/cm$^2$, and significant cell death occurred at >6 mg/cm$^2$. Based on these findings, it was concluded that the VCM level varies depending on the body and incision sizes, type of surgery, and patient factors, but that investigation of the minimum concentration for intrawound spray in vivo is necessary only for cases at high risk of emergence of VCM-resistant bacteria and a pseudoarthrosis.

In clinical cases, Ghobrial et al.[31] investigated 16 reports, in which intrawound VCM was administered in 6,701 of 9,721 cases, as described above. The mean SSI rates in the control and VCM-treated patients were 7.47 and 1.36%, respectively. Adverse events occurred in only 23 cases (0.3%) and these events were nephropathy (n=1), ototoxicity resulting in transient hearing loss (n=2), systemic absorption resulting in supratherapeutic vancomycin exposure (n=1), and culture-negative seroma formation (n=19). A high incidence of pseudoarthrosis in cases treated with local application of VCM powder has not been reported.

### *7. Ineffectiveness of intrawound VCM*

Finkelstein et al.[38] compared groups treated with 1 g of CEZ administered every 8 h and 1 g of VCM administered every 12 h as systemic antibiotic prophylaxis, with the aim of reducing the incidence of SSI with MRSA after coronary artery bypass grafting. The incidence of SSI was 9.0% and 9.5% using CEZ and VCM, respectively, with no significant difference, and SSI with coagulase-negative *Staphylococcus* occurred in many patients treated with VCM. Therefore, there was no effect of VCM on reducing the infection rate.

Tubiaki et al.[35] performed the initial RCT of intrawound VCM in control and treatment groups that both received standard systemic antibiotic prophylaxis with cefuroxime for spine surgeries. In the treatment group, 1 g of VCM was carefully sprayed on the subcutaneous region, fascia, and muscle layer while avoiding contact with the dura and bone graft after the wound was closed. The incidence of SSI was 1.68% (8/474) in the control group and 1.61% (7/433) in the treatment group, with no significant difference between the two groups. Martin et al.[34] investigated intrawound VCM for posterior cervical fusion surgery. The control and treatment groups received standard systemic antibiotic prophylaxis with CEZ, and 2 g of VCM was applied in the treatment group in the manner described above for Tubiaki et al. The incidence of SSI was 6.9% (12/174) in the control group and 5.2% (6/115) in the treatment group, again with no significant difference between the two groups.

Ghobrial et al.[33] reported their experience with intrawound VCM in spinal surgery at a single institution between 2011 and 2013. Standard systemic antibiotic prophylaxis with CEZ was performed, and 1-2 g of VCM was typically applied to the local site after the wound was closed. The amount of VCM used depended on the wound size, and 6 g was applied in rare cases. The mean amount used was 1.13 g (range 1-6 g). The rate of SSI was 6.71% (66/981). For comparison, the incidence of SSI was 3.4% (276/8122) at the same institution between 2005 and 2009, before introduction of VCM powder[41]. Thus, use of VCM powder appears to have increased the incidence of SSI at this institution.

### *8. Future prospects*

Application of intrawound VCM reduced the incidence of

SSI in many reports, but the amount and spray method varied. A dose of 1 or 2 g was commonly selected depending on the surgical wound size, but 0.5 and 6 g were used in some reports. The drug was sprayed with avoidance of the bone graft and dura in some reports, but not in others[42]. In most reports the VCM level was not measured in the surgical wound or serum. Careful administration with avoidance of contacting the bone graft and dura may result in VCM powder locally applied into wounds not reaching the bone graft region or dura. The drug may permeate the wound at a high level when the wound is closed. Surgical procedures and patient background with use of VCM powder also varied. Routine application in all spine surgeries is likely to promote emergence of resistant bacteria. Thus, it is necessary to investigate the background of patients to be treated, and to determine the intrawound VCM concentration required to prevent SSI and the amount of VCM needed to reach this concentration. Local application of VCM powder is currently not described in the package insert and is not approved by FDA. A multicenter RCT is needed to examine the safety and efficacy of this treatment.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

## References


1. Mangram SJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection. Infect Control Hosp Epidemiol 1999;20:247-78.
2. Masaoka T, Yamamoto K, Ishii Y, et al. Epidemiology of orthopaedic surgical site infection. Rinsho Seikei Geka 2009;44:975-80. (in Japanese)
3. Imajo Y, Taguchi T, Yone K, et al. Nationwide survey for spine surgery in Japan 2013. J Spine Res 2013;4:1367-79. (in Japanese)
4. Borkhuu B, Borowski A, Shah SA, et al. Antibiotic-loaded allograft decreases the rate of acute deep wound infection after spinal fusion in cerebral palsy. Spine 2008;33:2300-4.
5. Massie JB, Heller AG, Abittol JJ, et al. Post operative posterior spinal wound infections. Clin Orthop Relat Res 1992;284:99-108.
6. Rechtine GR, Bono PL, Cahill D, et al. Postoperative wound infection after instrumentation of thoracic and lumbar fractures. J Orthop Tauma 2001;15:566-69.
7. Sponseller PD, LaPorte DM, Hungerford NW, et al. Deep wound infections after neuromuscular scoliosis surgery: a multi-center study of risk factors and treatment outcomes. Spine 2000;25:2461-66.
8. Hodges SD, Humphreys SC, Eck JC, et al. Low postoperative infection rates with instrumented lumbar fusion. South Med J 1998; 91:1132-36.
9. Sasso RC, Garrido BJ. Postoperative spinal wound infections. J Am Acad Orthop Surg 2008;16:330-7.
10. ter Gunne AFP, Cohen DB. Incidence, prevalence, and analysis of risk factors for surgical site infection following adult spinal surgery. Spine 2009;34:1422-28.
11. Gerometta A, Olaverri JCR, Bitan F. Infections in spinal instrumentation. Int Orthop 2012;36:457-64.
12. Caroom C, Tullar JM, Benton EG Jr, et al. Intrawound vancomycin powder reduces surgical site infections in posterior cervical fusion. Spine 2013;38:1183-7.
13. Kim HS, Lee SG, Kim WK, et al. Prophylactic intrawound application of vancomycin powder in instrumented spinal fusion surgery. Korean J Spine 2013;10:121-5.
14. Strom RG, Pacione D, Kalhorn SP, et al. Lumbar laminectomy and fusion with routine local application of vancomycin powder: decreased infection rate in instrumented and non-instrumented cases. Clin Neurol Neurosurg 2013;115:1766-9.
15. Kirkland KB, Briggs JP, Trivette SL, et al. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infec Contorl Hosp Epidemiol 199;20:725-30.
16. Calderone RR, Garland DE, Capen DA, et al. Cost of medical care for postoperative spinal infections. Orthop Clin North Am 1996;27:171-82.
17. Godil SS, Parker SL, O'Neill KR, et al. Comparative effectiveness and cost-benefit analysis of local application of vancomycin powder in posterior spinal fusion for spine trauma. J Neurosurg Spoine 2013;19:331-5.
18. Khan NR, Thompson CJ, DeCuypere M, et al. A meta-analysis of spinal surgical site infection and vancomycin powder. J Neurosurg Spine 2014;21:974-83.
19. Sweet FA, Roh M, Silva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions. Spine 2011;36:2084-88.
20. Weinstein MA, McCabe JP, Cammisa FP Jr. Postoperative spinal wound infection: A review of 2391 concecutive index procedures. J Spinal Disord 2000;13:422-26.
21. Collins I, Wilson-MacDonald J, Chami G, et al. The diagnosis and management of infection following instrumented spinal fusion. Eur Spine J 2008;17:445-450.
22. Petilon JM, Glassman SD, Dimar JR, et al. Clinical outcomes after lumbar fusion complicated by deep wound infection. Spine 2012; 37:1370-74.
23. Chen SH, Lee CH, Huang KC, et al. Postoperative wound infection after posterior spinal instrumentation: analysis of long-term treatment outcomes. Eur Spine J 2015;24:561-70.
24. Shaffer WO, Baisden J, Fernand R, et al. Evidence-based clinical guidelines for multidisciplinary spine care. Antibiotic prophylaxis in spine surgery. NASS Evidence-Based Clinical Guidelines Committee. 2013 http://www.spine.org/Pages/PracticePolicy/ClinicalCare/ClinicalGuidelines/Default.aspx
25. Antibiotic Expert Group. Therapeutic Guidelines Antibiotic. 13th ed. Melbourne, Victoria, Australia: Therapeutic Guidelines Limited; 2006.
26. Clinical practice guideline: Antimicrobial prophylaxis for postoperative infection. Jpn. J. Chemother. 2016;64:153-232.
27. Melzer M, Eykyn SJ, Gransden WR, et al. Is methicillin-resistant staphylococcus aureus more virulent than methicillin-susceptible S. aureus? A comparative cohort study of British patients with nosocomial infection and bacteremia. CID 2003;37:1453-60.
28. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant staphylococcus aureus infections in the United States. JAMA 2007;298:1763-71.
29. Noskin GA, Rubin RJ, Schentag JJ, et al. National trends in staphylococcus aureus infection rates: impact on economic burden and mortality over a 6-year period (1998-2003). CID 2007;45: 1132-40.
30. Molinari RW, Khera OA, Molinari WJ. Prophylactic intraoperative powderd vancomycin and postoperative deep spinal wound infection: 1512 consecutive surgical cases over a 6-year period. Eur Spine J 2012;21:476-82.

**31.** Ghobrial GM, Cadotte DW, Williams Jr. K, et al. Complications from the use of intrawound vancomycin in lumbar spinal surgery: a systematic review. Neurosurg Focus 2015;39:E11.
**32.** Gaviola ML, McMillian WD, Ames SE, et al. A retrospective study on the protective effects of topical vancomycin in patients undergoing multilevel spinal fusion. Pharmacotherapy 2016;36:19-25.
**33.** Ghobrial GM, Thakkar V, Andrews E, et al. Intraoperative vancomycin use in spinal surgery. Spine 2014;39:550-55.
**34.** Martin JR, Adogwa O, Brown CR, et al. Experience with intrawound vancomycin powder for posterior cervical fusion surgery. J Neurosurg Spine 2015;22:26-33.
**35.** Tubaki VR, Rajasekaran S, Shetty AP. Effect of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients. Spine 2013; 38:2149-55.
**36.** Gans I, Dormans JP, Spiegel DA, et al. Adjunctive vancomycin powder in pediatric spine surgery is safe. Spine 2013;38:1703-1707.
**37.** Dennis HH, Wei DT, Darren KZ, et al. Is Intraoperative local vancomycin powder the answer to surgical site infections in spine surgery? Spine 2016; Epub ahead of print.
**38.** Finkelstein R, Rabino G, Mashiah T, et al. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcus infections. J Thorac Cardiovasc Surg. 2002;123:326-32.
**39.** Edin ML, Miclau T, Lester GE, et al. Effect of cefazolin and vancomycin on osteoblast in vitro. Clin. Orthop 1996;333:245-251.
**40.** Eder C, Stefan S, Trifinopoulos J, et al. Does intrawound application of vancomycin influence bone healing in spinal surgery? Eur Spine J 2016;25:1021-28.
**41.** Gruskay J, Smith J, Kepler CK, et al. The seasonality of postoperative infection in spine surgery. J Neurosurg Spine 2013;18:57-62.
**42.** Kang DG, Holekamp TF, Wagner SC, et al. Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. Spine J 2015;15:762-70.