SHORT COMMUNICATION

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Intrawound Vancomycin powder as the prophylaxis of surgical site infection after invasive spine surgery with a high risk of infection

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ABSTRACT

Surgical site infections (SSIs) are one of the most serious complications in spine surgery. We investigated the efficacy of locally administered vancomycin (VCM) powder for prophylaxis on SSI after invasive spine surgery. We retrospectively studied 174 consecutive patients who underwent spine surgery. In patients of the VCM group (n = 81), VCM powder was administered in the wound before closing wound. Patients who did not receive VCM treatment were set as a control group (n = 93). We compared the patients' background, operation time, intraoperative blood loss, usage of implants, presence of deep SSI, and side effects between the two groups. There were no significant differences between the groups in age, gender, and BMI. The operation time and the intraoperative blood loss were longer and greater in the VCM group than in the control group ($P < 0.005$, $P < 0.001$, respectively). Implants were used in 85% of the VCM group, and in 31% of the control group ($P < 0.001$). Deep SSI was not observed in the VCM group, whereas it was observed in 4 patients in the control group. No side effects were observed in any of the cases. In conclusion, surgeons applied VCM for cases which were invasive or had a high risk of infection. However, deep SSI was not observed in anyone in the VCM group. The intrawound administration of VCM might be effective to prevent SSI in cases with high risks of infection.

Keywords: surgical site infection, vancomycin hydrochloride, intrawound administration, local administration, spine surgery

Surgical site infections (SSIs) are one of the most serious complications of spine surgery. The incidence rate of deep SSI after spine surgery is reported to be 1-14%,[1)] with most of the causative bacteria being vancomycin (VCM)-susceptible.[2)] Additional surgery for debridement or the removal of instrumented materials might be necessary when antibiotic therapy for SSI is not effective. However, both surgical debridement and failed antibiotic treatment result in long-term hospitalization. It has been frequently reported that local application of VCM powder to wounds

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is effective after spine surgery;[3-5] however, its effectiveness in cases with a high risk of infection is still controversial. In this study, we investigated the efficacy of locally applied VCM powder in the prevention of SSIs after spine surgery.

METHODS

We studied patients who had spine surgery in our hospital from August 2014 until April 2016. However, patients who had surgery for existing infections were excluded from the study. Therefore, we studied 174 patients (mean age, 49 ± 23 years old; 79 males and 95 females) retrospectively. The Institutional Review Board of Nagoya University Graduate School of Medicine approved the off-label use of intrawound VCM (No. TF15003) and the study design (No.355-2). This study was carried out after obtaining the consent of each participant. The patients received identical standard operative and post-operative care procedures based on protocolized department guidelines. All the patients planned to use implant (n = 98, 56.3%) were routinely screened for nasal colonization by methicillin-resistant *Staphylococcus aureus*; however, none of the case was positive. Patients with diabetes underwent perioperative glycemic control, which was performed by endocrinologists. Surgical sites were prepped with 10% iodine more than three times and covered with iodine-containing dressing preoperatively. Cefazolin sodium (1 g) was administered as an intravenous infusion within 60 min before the start of surgery, and then every three hours during surgery. No patient was administered intravenous VCM prior to or during surgery. During surgery, anesthesiologists performed glycemic control. The target blood glucose level was less than 200 mg/dL. Normothermia was maintained in all patients. In patients who received VCM treatment (VCM group), either 1 g (adult) or 0.5 g (child < 12 years) of VCM hydrochloride powder was applied to the wound and bone grafts before the wound was closed. Patients who did not receive VCM treatment were used as a control group. In both groups, drain tubes were placed in the wound for a minimum of two days, and removed if the drainage was less than 100 ml/day. We examined the following items and compared them between the two groups: patients' background, use or non-use of immunosuppressant, surgery duration, intraoperative blood loss, duration of wound drainage, use or non-use of implants, number of fused vertebrae, presence or absence of deep SSI based on World Health Organization criteria,[6] and the occurrence of adverse effects (allergies, renal failure, red man syndrome, or auditory disorders) associated with VCM use.

For statistical analysis, we performed a Chi-square test, a Fisher's exact test, and a *t*-test. P values less than 0.05 were considered statistically significant. The data have been presented as mean ± standard deviation.

RESULTS

There were 81 patients in the VCM group and 93 patients in the control group. All patients were followed more than one year. Follow up period (mean ± standard deviation) was 20.4 ± 6.5 months in the VCM group and 22.5 ± 6.6 months in the control group ($p = 0.43$). All surgeries were performed by or under the supervision of three skilled faculty surgeons (SI, KA, and KK). The primary surgeon did not differ between the groups (p = 0.72). The demographic and surgery data of the patients are shown in Table 1. There were no significant differences between the groups in mean age, gender ratio, and body mass index ($p = 0.62$, $p = 0.88$, and $p = 0.48$, respectively). Immunosuppressants other than oral steroids were not administered to

any patient. There was no significant difference in the use of oral steroids between the groups (p = 0.60). The VCM group showed significantly higher values in the mean surgery duration and intraoperative blood loss than the control group ($p < 0.005$ and $p < 0.001$, respectively). There was no significant difference in the duration of drainage (p = 0.18). Implants were used in 85% and 31% of the patients in the VCM and control groups, respectively ($p < 0.001$). The numbers of fused vertebrae in patients with implants (n = 98) were 7.0 ± 4.8 and 4.5 ± 3.4 in the VCM and control groups, respectively ($p < 0.01$). The incidence of deep SSI was 0% in the VCM group and 4.3% (4 patients) in the control group (Table 2). The following causative bacteria were detected in the infection cases: methicillin-resistant *Staphylococcus aureus* (1 case), methicillin-resistant *Staphylococcus epidermidis* (2 cases), and *Escherichia coli* (1 case). All of Staphylococcus strains were VCM susceptible. Two of the infected patients received successful conservative treatment with antibiotics; however, in the other two cases, additional debridement surgery had to be performed. No adverse effects (allergies, renal failure, red man syndrome, auditory disorders and local soft tissue problems) usually associated with the use of VCM were observed in any of the cases.

DISCUSSION

The results showed that the duration of surgery, blood loss rate, rate of implant use, and the number of fused vertebrae were longer or higher in the VCM group than they were in the control group. We found that the surgeons tended to apply VCM into the wounds when the surgery was

Table 1 Demographic and surgery data of the patients.

	Control group	VCM group	p value
Number of cases	93	81	
Male ratio	46%	44%	0.81
Age (years)	50.3 ± 22.2	48.4 ± 23.8	0.60
Body mass index (kg/m^2)	22.0 ± 4.7	22.6 ± 5.9	0.81
Diabetes	11%	42%	< 0.001
Use of oral steroid	1.1%	2.4%	0.60
Surgery duration (min)	199 ± 93	266 ± 127	< 0.005
Blood loss (ml)	198 ± 252	726 ± 725	< 0.001
Duration of drainage (days)	2.3 ± 0.6	2.4 ± 0.6	0.18
Revision surgery case	7.5%	13.6%	0.19
Implant usage	31%	85%	< 0.001
Number of fused vertebrae (in cases with implants)	4.5 ± 3.4	7.0 ± 4.8	< 0.01
Details of spinal disorder (number)			< 0.001
Scoliosis	14	30	
Degenerative disease	25	17	
Spinal cord tumor	46	14	
OPLL	6	16	
Others	2	4	

VCM, vancomycin; OPLL, ossification of the posterior longitudinal ligament.

Table 2 Details of patients with deep surgical site infection.

Group	Age (y), sex	Bacterial strain	Disease / surgery	Surgery duration (min) / blood loss (ml)	Treatment for infection
Control	35 / female	*E. coli*	Lumbar vertebral tumor / Revision posterior fusion	409 / 454	Debridement
Control	55 / female	MRSE	Degenerative lumbar listhesis / PLIF	105 / 400	Debridement, cage removal
Control	68 / male	MRSE	Degenerative lumbar listhesis / Revision PLIF	363 / 630	Non-surgical treatment
Control	72 / male	MRSA	Cervical spondylotic myelopathy / Laminoplasty	90 / 60	Non-surgical treatment

E. coli, *escherichia coli*; MRSE, methicillin-resistant *staphylococcus epidermidis;* MRSA, methicillin-resistant *staphylococcus aureus*; PLIF, posterior lumbar interbody fusion.

invasive or had a high risk of infection. Although there was a high risk of developing infections in many of the cases, deep SSI was not observed in the VCM group. To our knowledge, this report is the first to indicate the efficacy of intrawound VCM treatment after spine surgery in Japanese patients.

There is little evidence of local VCM application in the prophylaxis of SSI in cases with a high risk of infection. Tubaki et al. reported that local application of VCM to surgical wounds did not significantly reduce the incidence of infection after spine surgery in a randomized controlled study.[7] In that study, there were limitations such as the lack of power analysis and a low infection rate (1.61-1.68%), which indicated that the risk of developing an infection was relatively low. Various retrospective studies have reported decreased relative risks for SSI (0.086-0.23) and safety after intrawound use of VCM.[3-5] On these basis, intrawound VCM treatment is recommended in pediatric spine surgery guidelines.[8]

The biggest concern about intrawound VCM is its safety. Sweet et al. studied the serum level of VCM after intrawound application of 2 g VCM in 178 patients who had undergone spine surgery. The minimum sensitivity of the blood test to VCM was 0.6 μg/ml in that study. The results showed that VCM was not detected in serum in 80% of the patients. In 20% of the patients in whose serum VCM was detected, the average VCM level was 1.6 μg/ml at postoperative day 1.[3] The serum level was quite low compared to the recommended safety margin of VCM (< 15 μg/ mL).[9] The molecular mass of VCM is high; therefore, it is not easily absorbed into the blood,[3] and the risks of its side effects, such as renal failure and red man syndrome, are quite low.[3-5,7] Although none of the case measured the serum concentration of VCM, no adverse effects were observed in the current study. Furthermore, it has been reported that an effective concentration of VCM is detected in wound drainage on the third day after surgery.[3]

It has been reported that, in clinical settings, no differences are observed in pseudoarthrosis rate with or without local VCM powder application after posterior cervical fusion.[4] Furthermore, it has been shown that VCM does not suppress *in vitro* proliferation of human osteoblasts[10] or delay *in vivo* bone fusion in posterior lumbar fusion in rats.[11] These indicate that intrawound VCM would not obstruct bone healing.

There were several limitations in this study. Firstly, patients' background information and surgical interventions were different between the VCM and control groups. In addition, there was a large selection bias. The surgeons tended to use VCM in cases where the risk of infection

was high. Since we did not set strict criteria for the application of intrawound VCM, VCM use was the surgeon's choice. Because patients in the VCM group had a higher risk of developing infections and underwent more invasive surgeries than those in the control group did. Therefore, we might have biased for the effect of VCM in preventing SSIs. Another limitation was the small number of subjects used in the study. As a result, the statistical power was not high enough to compare the occurrence of SSIs between the two groups. We therefore plan to conduct a randomized controlled trial with an adequate number of cases.

In conclusion, the intrawound application of VCM powder might be safe and effective in preventing SSIs after spine surgeries in cases with a high risk of infection.

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CONFLICT OF INTEREST

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