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Clinical Study

The efficacy of intrawound vancomycin powder and povidone-iodine irrigation to prevent surgical site infections in complex instrumented spine surgery

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Abstract

BACKGROUND CONTEXT: Surgical site infections (SSIs) are notorious complications in spinal surgery and cause substantial patient morbidity. Intraoperative decontamination of the wound with povidone-iodine irrigation or vancomycin powder has gained attention lately, but the efficacy of either intervention is unclear.

PURPOSE: To determine the efficacy of intrawound povidone-iodine or vancomycin in reducing the incidence of deep- and superficial SSIs in instrumented spinal surgery.

STUDY DESIGN/SETTING: Retrospective cohort study.

PATIENT SAMPLE: A retrospective chart review was performed including all consecutive adult patients undergoing open, posterior, instrumented spinal surgery at any level between January 2012 and August 2017.

OUTCOME MEASURES: The presence of SSI was evaluated according to the criteria published by the Centers for Disease Control and Prevention. The SSIs were divided into deep SSIs (below the muscular fascia) and superficial SSIs (above the muscular fascia).

METHODS: A retrospective cohort without intrawound treatment was compared with two separate, consecutive intervention groups. One intrawound group received 1.3g/L povidone-iodine irrigation and the other received 1-2 grams of intrawound vancomycin powder at the end of surgery. Incidence of SSIs, as well as demographic, surgical and patient-related variables were registered and compared between groups. In patients with SSI, additional microbiological data were collected.

RESULTS: In total, 853 patients were included. In the control group (N=257), 25 (9.7%) patients developed a deep and 13 (5.1%) developed a superficial SSI. In the povidone-iodine group (N=217), 21 (9.7%) patients developed a deep and two (0.9%) developed a superficial SSI. Compared with the control group, there was no significant difference in the incidence of deep SSIs (risk ratio [RR]: 1.00, 95% CI 0.57−1.73), although the number of superficial SSIs was reduced significantly (RR 0.18, 95% CI 0.04−0.80). In the vancomycin group (N=379), 19 (5.0%) patients developed a deep and six (1.6%) developed a superficial SSI. Both deep (RR: 0.52, 95% CI 0.29−0.92) and superficial SSIs (RR: 0.31, 95% CI 0.12−0.81) were significantly reduced in the vancomycin group compared with the control group, even when correcting for several risk factors associated with SSIs in a multivariable logistic regression analysis. There were no significant differences in complications between the 3 groups. No gram-negative selection or vancomycin-resistance was seen in the vancomycin group.

FDA device/drug status: Not applicable.

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CONCLUSIONS: Intrawound application of vancomycin was associated with a significant reduction in both deep and superficial SSIs in instrumented spinal surgery. A 1.3g/L intrawound povidone-iodine solution did not show a reduction in deep SSIs, although a reduction of superficial SSIs was observed.

Keywords: Spine; Surgical site infection; Postoperative infection; Prevention; Prophylaxis; Intrawound; Intra-wound; Intra-site; Povidone-iodine; Vancomycin

Introduction

Surgical site infections (SSIs) are notorious complications in instrumented spinal surgery. The SSIs can be classified according to the Centers for Disease Control and Prevention (CDC) classification into superficial SSIs (superficial to the muscular fascia), deep SSIs (deep to the muscular fascia), and organ/space SSIs [1]. Especially, these last two categories cause substantial patient morbidity, leading to prolonged hospital stay, a substantial loss of quality of life and high medical costs [2,3].

Previously, many studies addressed the use of intrawound treatments for the prevention of SSIs in spinal surgery. In an attempt to thoroughly decontaminate the wound, surgeons frequently use powdered vancomycin [4−6] or solutions of antiseptics [7,8] before closure. It is still debated whether these approaches are effective and which method is to be preferred. Many retrospective studies show a good effect of both interventions, although the quality of these studies is usually moderate to low [9].

Antiseptics are commonly preferred to antibiotics especially in light of the prevention of antimicrobial resistance. Therefore, in a previous in vitro study, we focused on SSI reduction with intrawound antiseptics and determined that povidone-iodine provided the optimal balance between bactericidity and cytotoxicity [10]. Based on that study, we started using povidone-iodine irrigation at a concentration of 1.3g/L for clinical use in high risk, instrumented, complex spine surgery. However, we did not achieve our goal of substantial reduction in SSIs after 1 year and therefore switched to 1 to 2 grams of intra wound vancomycin powder, which was shown to be effective in several other studies [4,11,12].

In the current study we aimed to determine whether the application of intrawound povidone-iodine solution or vancomycin powder reduced the incidence of deep and/or superficial SSIs compared with a historical control group when used in addition to standard intravenous (IV) antibiotic prophylaxis. Secondary aims were to determine if either intervention was associated with adverse effects and to determine whether there were differences in microbiological culture results (cultured micro-organisms, differences in antimicrobial resistance patterns) between the three cohorts. Finally, we wanted to ascertain whether differences in SSI rates were only caused by the intrawound treatments. To do this, we investigated how the SSI rate of other orthopedic implant cohorts at our institution that were not treated with these intra-wound prophylaxes changed over time.

Materials and methods

Ethical review and study design

A waiver for ethical review was granted by the Institutional Review Board of the University Medical Center Utrecht. We performed a retrospective cohort study according to the "Strengthening the reporting of observational studies in epidemiology" statement, with patients undergoing instrumented spinal surgery from January 2012 up to and including August 2017 at a single academic hospital. Two consecutive, experimental cohorts were compared with a historical control cohort.

All consecutive adult patients undergoing instrumented spinal surgery were evaluated. We included high risk procedures, defined as open (not percutaneous), posterior surgery lasting at least 2 hours (skin-to-skin time). Patients not conforming to these criteria were excluded. Patients with a previous or current spinal infection (ie, deep or superficial SSI, spondylodiscitis, epidural abscess) and patients with fewer than 3 months of follow-up (unless SSI presented earlier than 3 months) were also excluded.

Study groups

Between 2012 and 2014, no intrawound treatments were used in instrumented spinal procedures, and only the standard antimicrobial prophylaxis (as described in "Standard antimicrobial prophylaxis and surgical treatment") was available. The patients in this period were the control group. Starting in March 2014, in addition to the standard peri-operative interventions, all included patients were irrigated with a 500 mL povidone-iodine solution at a concentration of 1.3g/L. At the end of surgery, the surgical wound was filled with this solution for 2 minutes. Thereafter, the wound was irrigated with saline. From June 2015 onwards, the povidone-iodine irrigation solution was replaced with intrawound vancomycin powder. In these patients, after saline irrigation, vancomycin powder (Vancomycin, Xellia Pharmaceuticals, Copenhagen) was spread into all layers of the deep and superficial surgical wound, the instrumentation, the dura and the bone graft. In most surgical wounds, 1000 mg was satisfactory to cover the entirety of the wound with powder. If the size of the wound was especially large, up to 2000 mg of vancomycin was used.

Standard antimicrobial prophylaxis and surgical treatment

The patients in all three groups underwent preoperative *Staphylococcus aureus* nasal decontamination with mupirocin (Bactroban, GlaxoSmithKline, Brentford) and skin antisepsis with chlorhexidine gluconate (Hibiscrub, BCM Ltd., Nottingham) from one day preoperatively until four days postoperatively. All surgery was performed in laminar airflow operating theatres. Before surgery, the skin was cleaned with chlorhexidine gluconate and the patient was covered with disposable drapes. During surgery, all patients received standard antibiotic prophylaxis with 2000 mg IV cefazolin within 1 hour before incision. An additional dose of 1000 mg was given in surgeries lasting longer than 4 hours and cefazolin was continued during the first postoperative day with 1000 mg given every 6 hours. During surgery, a standard midline incision and open approach was used. When bone graft was used, it was autologous bone harvested from the spine during the operation. No allograft bone products were used. After copious sterile saline irrigation by gravity, the wound was closed in layers, the skin with either sutures or staples and the wound was covered with a hydrocolloid dressing (AQUACEL Surgical, Convatec, Deeside).

At our institution, all instrumented patients with a suspected deep SSI (based on the CDC criteria) are reoperated for extensive irrigation and debridement, followed by antimicrobial therapy. Superficial SSIs are treated with antibiotics only.

Data extraction and outcomes

Data was extracted from the electronic medical records using a standardized form. Patient data included sex and age, history of previous spinal surgery, American Society of Anesthesiologists physical status score, body mass index, presence of diabetes mellitus and smoking status. Surgical details included the procedure date, indication for surgery, whether surgery was elective or emergency (<3 hours, <8 hours, and <24 hours), length of procedure (from incision to end of closure), number of instrumented levels, instrumented location (cervical, thoracic, lumbar) and follow-up length.

The presence of SSI was determined through the application of SSI criteria published by the CDC [1]. In patients that suffered an SSI, additional data were collected. These included date of onset, type of SSI (superficial or deep, organ/space SSIs were classified as deep), and microbiological culture results. In addition, patient records were searched for adverse events possibly related to intrawound treatments: prolonged wound leakage and wound healing problems, nonunion (based on clinical symptoms or evident signs of implant loosening on imaging), anaphylactic or hypersensitive drug reactions and specific reactions known to be related to vancomycin like nephrotoxicity, (transient) hearing loss, and culture negative seroma [13].

During the vancomycin cohort, new operating theaters were introduced at our institution (Fig. 1). To investigate whether this, or any other measure introduced during the treatment cohorts, reduced the risk of SSI irrespective of intrawound treatment, we determined the SSI rate in four orthopedic patient groups that did not use intrawound treatments during the study periods. We included all primary and revision total hip arthroplasties (THA) and total knee arthroplasties (TKA) performed at our institution from 2 years before until 2 years after the new operating theaters were put into commission and compared the SSI rates of these groups before and after introduction of the new operating theaters.

Statistical analysis

Normality of data was assessed by visual inspection of normality plots. Mean (with standard deviation) or median (with interquartile range; IQR) of continuous variables were reported for each group. To study differences in baseline characteristics between groups, three-way Pearson χ^2

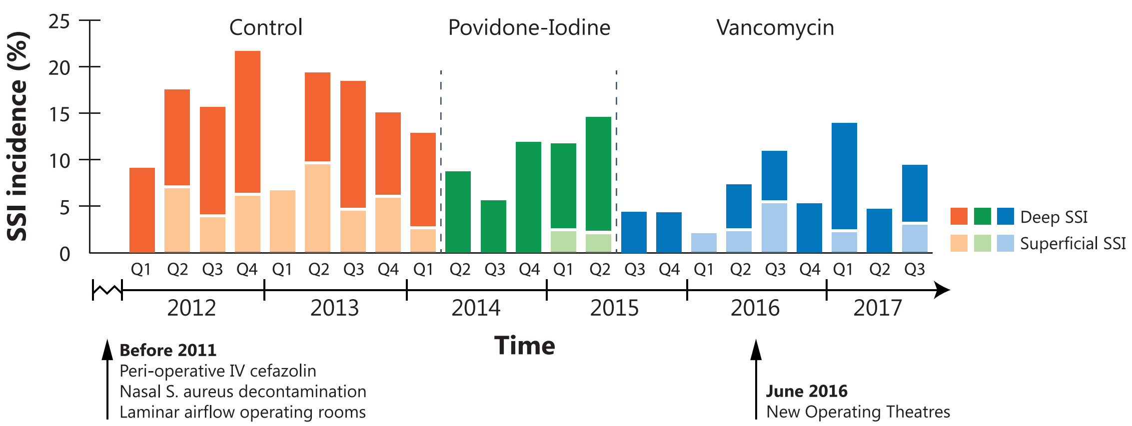

Fig. 1. SSI rate over time.Each bar represents 3 months. The arrows represent the introduction of new peri-operative measures that may have influenced the SSI incidence.

tests were performed for categorical variables and one-way analysis of variance (parametric data) or Kruskal-Wallis tests (nonparametric data) were performed for continuous measurements. Post-hoc testing was performed in cases in which variables differed significantly between groups. We performed two-tailed Pearson χ^2 tests to determine whether there were statistical differences in the number of deep- and superficial SSIs between the study groups. The risk ratio (RR) was used as the outcome measure of choice. A RR below one signified a lower risk for the povidone-iodine- or vancomycin cohort compared with the control cohort. To determine whether observed group differences were present irrespective of other potential risk factors, a multivariable logistic regression was performed. The dependent outcome evaluated was SSI (either deep or superficial). Several known risk factors for SSI were added to the model as independent variables. These included (1) age, (2) American Society of Anesthesiologists classification, (3) presence of diabetes mellitus, (4) number of instrumented levels, (5) length of procedure, (6) previous spinal surgery, (7) tobacco use, and lastly, (8) type of intrawound treatment. Care was taken so that the number of events (SSIs) per included variable did not exceed 10, to reduce the risk of bias in the model [14]. Odds ratios with 95% confidence intervals (CI) were calculated for each variable. Statistical significance was set at p<0.05. Statistical analyses were performed with IBM SPSS Statistics 24 (Chicago, SPSS Inc.).

Results

A total of 1,290 consecutive instrumented spinal surgery cases were evaluated. After exclusion of low-risk patients, patients with a spinal infection, and patients with insufficient follow-up, a total of 853 patients were included for analysis. The control cohort included 257 patients, the povidone-iodine cohort included 217 patients and the vancomycin cohort included 379 patients.

Baseline variables between groups are found in Table 1. All three groups were statistically similar regarding age, sex, and most other patient-related and surgical characteristics. There were statistically significant differences between groups when regarding follow-up length (p<0.001), with the control cohort having the longest follow-up time (20.0 IQR 25.0 months) and the vancomycin cohort having the shortest (12.0 IQR 6.0 months). Other significant differences were found in the indication for surgery (p=0.001) with more degenerative cases in both the povidone-iodine and vancomycin group compared with controls and fewer cases operated for instrumentation failure/malposition in the povidone-iodine cohort. In addition, the povidone-iodine cohort had fewer levels fused than the vancomycin group (p=0.032). The control cohort had significantly more fusions to the ilium compared with the experimental cohorts.

The incidence of deep and superficial SSIs in the three groups can be found in Table 2. In the control group of 257 patients, 25 (9.7%) developed a deep and 13 (5.1%) developed a superficial SSI. In the povidone-iodine group of 217 patients, 21 (9.7%) developed a deep and two (0.9%) developed a superficial SSI. Compared with the control group, there was no significant difference in the incidence of deep SSIs (RR: 1.00, 95% CI 0.57−1.73), although the incidence of superficial SSIs was significantly reduced (RR: 0.18, 95% CI 0.04−0.80). The number needed to treat (NNT) for povidone-iodine to prevent a single superficial SSI was 24, indicating that 24 patients need to be treated with povidone-iodine to prevent one superficial SSI. In the vancomycin group of 379 patients, 19 (5.0%) developed a deep and 6 (1.6%) developed a superficial SSI. Both the incidence of deep as well as superficial SSIs was significantly reduced compared with the control group. The incidence of deep SSIs nearly halved compared with the control cohort (RR: 0.52, 95% CI 0.29−0.92). This corresponded to an NNT of 22. There was also a significant reduction in the number of superficial SSIs (RR: 0.31, 95% CI 0.12−0.81), with an NNT of 29. The results of the multivariable logistic regression analysis can be seen in Table 3. The significant protective effect of vancomycin on SSIs remained when correcting for several risk factors. Patients receiving intrawound vancomycin had 0.38 times the odds of developing SSIs compared with the control group. An overview of the SSI rate over time (and in relation to introduction of SSI prophylactic interventions) can be seen in Fig. 1.

The median time between surgical procedure and SSI onset was 16 days (IQR 12) for superficial and 13 days (IQR 11) for deep SSIs. The time between surgery and onset of deep SSIs differed significantly between groups (p=0.043). The intrawound cohorts showed an increase in median time between surgery and onset of deep SSIs compared with controls (control: 10 days, povidone-iodine: 14 days, vancomycin: 16 days). Microbiological results from SSI patients can be seen in Fig. 2a. About half of the SSI patients suffered from a polymicrobial SSI. The frequencies of all cultured micro-organisms in SSI patients (including those in polymicrobial SSIs) are reported in Fig. 2b. We observed no SSIs with vancomycin-resistant micro-organisms (eg, vancomycin-resistant enterococci or vancomycin-resistant staphylococcus aureus) in the vancomycin group, and the rate of MRSA remained consistently low throughout the study period. The SSIs caused by gram-negative micro-organisms (including those in polymicrobial cultures) were found in 3.5% of all patients in the control group, 2.3% of all patients in the povidone-iodine group and 2.1% of all patients in the vancomycin group (p=0.531).

Two of the patients in the vancomycin group (0.5%) had an episode of postoperative acute kidney injury (AKI) that recovered with IV hydration. The first patient had a history of chronic kidney disease and developed a marked rise in serum creatinine the first postoperative day (85 μmol/L−

Table 1
Baseline characteristics

	Cohort			
	Control (n=257)	Povidone-iodine (n=217)	Vancomycin (n=379)	p value
Median age (years)	58.0 IQR 19.0	59.0 IQR 21.0	60.0 IQR 19.0	0.350
Male	127 (49.4%)	114 (52.5%)	191 (50.4%)	0.789
Median operative length (min)	185.0 IQR 94.0	190.0 IQR 97.0	196.0 IQR 88.0	0.367
Timing of the procedure				0.091
Elective	213 (82.9%)	172 (79.3%)	280 (73.9%)	
Emergency < 24 h	8 (3.1%)	5 (2.3%)	10 (2.6%)	
Emergency < 8 h	34 (13.2%)	34 (15.7%)	76 (20.1%)	
Emergency < 3 h	2 (0.8%)	6 (2.8%)	13 (3.4%)	
ASA score				0.223
1	62 (24.1%)	49 (22.6%)	76 (20.6%)	
2	128 (49.8%)	126 (58.1%)	203 (53.6%)	
3	65 (25.3%)	42 (19.4%)	92 (24.3%)	
4	2 (0.8%)	0	6 (1.6%)	
Smoking history	110 (42.4%)	92 (42.4%)	147 (46.2%)	0.916
Diabetes mellitus	30 (11.7%)	31 (14.3%)	38 (10.0%)	0.295
Mean BMI (kg/m^2)	25.6 ± 4.5	26.4 ± 5.1	25.8 ± 4.5	0.944
Indication for surgery (%)				**0.001**
Degenerative	63 (24.5%)	80 (36.9%)[C]	129 (34.0%)[C]	
Trauma	51 (19.8%)	48 (22.1%)	76 (20.1%)	
Osteoporotic fracture	16 (6.2%)	16 (7.4%)	10 (2.6%)	
Malignancy/Metastasis	51 (19.8%)	28 (12.9%)	69 (18.2%)	
Deformity	40 (15.6%)	23 (10.6%)	53 (14.0%)	
Nonunion	24 (9.3%)	20 (9.2%)	19 (5.0%)	
Instrumentation failure/malposition	12 (4.7%)[P]	2 (0.9%)	23 (6.1%)[P]	
Previous spinal surgery (%)	84 (32.7%)	65 (30.0%)	120 (31.7%)	0.814
Median no. levels fused	4.0 IQR 4.0	3.0 IQR 3.0	4.0 IQR 4.0[P]	**0.032**
Median follow-up (months)	20.0 IQR 25.0[P,V]	14.0 IQR 12.0[V]	12.0 IQR 6.0	**<0.001**
Operated area*				
Cervical	69 (26.9%)	83 (38.2%)	132 (34.8%)	0.066
Thoracic	149 (58.0%)	106 (48.8%)	232 (61.2%)	0.052
Lumbar	142 (55.2%)	103 (47.5%)	193 (50.9%)	0.468
Sacral	38 (14.7%)	34 (15.7%)	52 (13.7%)	0.803
Ilium	9 (3.5%)[P,V]	1 (0.5%)	3 (0.8%)	**0.040**
Median time between surgery and SSI (days)				
Superficial SSIs	13 IQR 13	20 IQR 0	20 IQR 9	0.118
Deep SSIs	10 IQR 5	14 IQR 9	16 IQR 15[C]	**0.043**

[C] Significantly higher than control group in post-hoc testing
[P] Significantly higher than povidone-iodine group in post-hoc testing
[V] Significantly higher than vancomycin group in post-hoc testing
* Multiple area's possible per patient. Significance testing was done by individual per-level χ^2 testing with Holm-Bonferroni multiplication of p values.
Statistically significant values are in bold.

Table 2
Surgical site infection results

	Cohort						
	Control (N=257)	Povidone-iodine (N=217)			Vancomycin (N=379)		
	Incidence	Incidence	p value	Risk	Incidence	p value	Risk
Deep SSI	25 (9.7%)	21 (9.7%)	0.985	RR 1.00 (95% CI 0.57−1.73)	19 (5.0%)	**0.021**	RR 0.52 (95% CI 0.29−0.92)
Superficial SSI	13 (5.1%)	2 (0.9%)	**0.010**	RR 0.18 (95% CI 0.04−0.80)	6 (1.6%)	**0.012**	RR 0.31 (95% CI 0.12−0.81)

Each experimental cohort risk was compared with the control cohort. Statistically significant values are in bold.

105 μmol/L), most likely caused by dehydration. Renal function improved over the course of 1 week with IV hydration. The second patient developed AKI 4 days following irrigation and debridement of a deep SSI (from 86 μmol/L at day 1 to 190μmol/L at day 4). This patient also used flucloxacillin (known to be able to cause AKI) as antibiotic SSI treatment. There was no AKI in the initial surgery of this patient (in which intrawound vancomycin was

Table 3
Multivariable logistic regression results

Variable		Slope	Standard error	Odds Ratio	p value
Age*		0.013	0.009	1.01 (95% CI 1.00-1.03)	0.139
ASA	ASA II†	0.305	0.381	1.36 (95% CI 0.64-2.86)	0.423
	ASA III−IV†	0.916	0.407	2.50 (95% CI 1.13-5.55)	**0.024**
Diabetes mellitus‡		0.068	0.337	1.07 (95% CI 0.55-2.07)	0.840
Instrumented levels*		0.065	0.042	1.07 (95% CI 0.98-1.16)	0.123
Length of procedure*		0.002	0.002	1.00 (95% CI 1.00-1.01)	0.217
Previous spinal surgery§		−0.196	0.261	0.82 (95% CI 0.49-1.37)	0.454
Tobacco use‖		0.153	0.238	1.17 (95% CI 0.73-1.86)	0.521
Treatment	Povidone-iodine¶	−0.362	0.291	0.70 (95% CI 0.39-1.23)	0.213
	Vancomycin¶	−0.964	0.277	0.38 (95% CI 0.22-0.66)	**<0.001**

* Continuous variables.
† Compared with ASA I.
‡ Compared with nondiabetics.
§ Compared with no previous spinal surgery.
‖ Compared with nontobacco users.
¶ Compared with control group.Intercept: −3.662, standard error of intercept: 0.660.An odds ratio < 1 denotes lower SSI odds for the investigated variable, an OR > 1 denotes greater SSI odds for the investigated variable. Statistically significant values are in bold. High ASA score and vancomycin treatment were both associated with significantly lower SSI odds when correcting for all other risk factors.

also used). After switching flucloxacillin to daptomycin, kidney function improved. Therefore, it is unlikely that the use of vancomycin was the eliciting factor of the AKI in either of these cases.

Five patients (1.3%) in the vancomycin cohort had culture negative seroma, which was not statistically significant compared with the other study groups. No other suspected adverse events that could be related to povidone-iodine- or vancomycin use were identified. The number of wound problems (prolonged leakage, slow wound healing) and nonunions were similar in all three cohorts.

The SSIs rates in the four other orthopedic groups before and after the introduction of the new operating theaters are shown in Table 4. In general, an increase in SSIs was seen in both THA and TKA over time (after introduction of the new operating theatres), both for primary as well as revision surgeries.

Discussion

We followed a rational pathway to address the high rate of SSIs that we observed in complex instrumented spine surgery. First, we aimed to reduce SSIs with intrawound povidone-iodine, but we changed this strategy when we did not observe the desired reduction in deep SSIs. After intrawound vancomycin prophylaxis, the incidence of deep SSIs dropped from 9.7% to 5.0%. In addition, the number of superficial SSIs significantly decreased to below 2%. These results are in line with other studies and make vancomycin a cost-effective intervention to reduce SSIs [9].

The povidone-iodine concentration of 1.3g/L was initially used because it offered the best balance between bactericidity and cytotoxicity, based on previous in vitro research [10]. This concentration is considerably lower than the concentration used by others that did find povidone-iodine effectiveness [7,8]. One explanation for this is that the in vitro situation is highly different from the actual wound environment. Certain factors in real wounds, like plasma proteins and hematogenous cells can dilute or neutralize the povidone-iodine, which would mean that the optimal balance between cytotoxicity and bactericidity is actually present at higher concentrations [15]. Evidence to support this comes from two RCTs that used intrawound povidone-iodine in spinal surgery in concentrations of 3.5 g/L, which is 2.5 times higher than the concentration used in the current study [7,8]. Their deep SSI rates dropped from 4.8% [7] and 2.9% [8] to 0%, with no apparent increase in nonunions. It is possible that our concentration was simply too low to be able to eliminate all micro-organisms. Therefore, further research on (different concentrations of) intrawound povidone-iodine is necessary.

Antimicrobial resistance is a concern when using antibiotics. Unfortunately, it is unknown if and how this affects patients undergoing intrawound treatment as research into this phenomenon is limited. In a prior study of complications following intrawound vancomycin, microbiological results of SSIs in patients treated with vancomycin did not show a significant increase in vancomycin-resistant strains, although there seemed to be a trend toward more SSIs caused by gram-negative bacteria [16]. No gram-negative selection was seen in the current study, which contradicts the above study as well as a recently published meta-analysis on microbial selection following intrawound vancomycin [17]. Curiously, the vancomycin cohort also suffered from fewer infections by gram-negative micro-organisms, although this difference was not statistically significant. Because vancomycin has a strictly gram-positive spectrum, this cannot be explained by the activity of the antibiotic. To reduce SSIs caused by gram-negative micro-organisms, additional prophylactic treatment is necessary. Basic science studies suggest that tobramycin (among other alternatives) could be added as an adjunct to vancomycin, because it provides gram-negative coverage

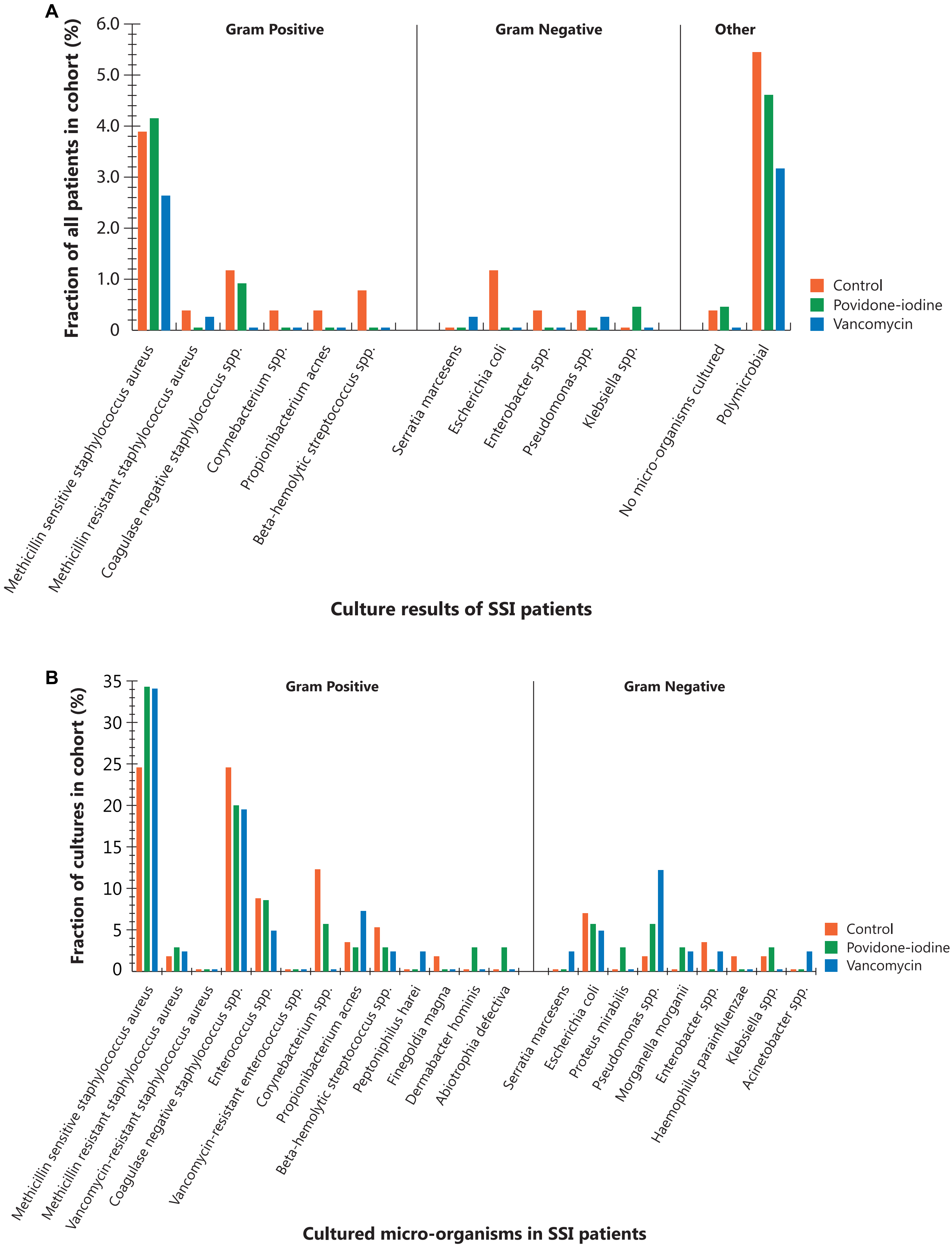

Fig. 2. Culture results of SSI patients. (A) Illustrates how many SSI patients in each cohort received a specific culture result. Results reported as fraction of total number of patients in cohort. (B) Cultured micro-organisms in SSI patients. Illustrates how frequent certain micro-organisms were cultured in SSI patients in each cohort. Results are reported as fraction of total number of cultured micro-organisms in cohort. Also includes all micro-organisms in polymicrobial SSIs.

Table 4
Surgical site infection incidence before and after introduction of new operating theatres

Group	SSI incidence 2 y before new operating theatres	SSI incidence 2 y following new operating theatres
Primary total hip arthroplasty	2.8% (4/145)	5.7% (9/158)
Primary total knee arthroplasty	2.3% (2/86)	2.4% (3/125)
Revision total hip arthroplasty	9.5% (2/21)	13.8% (4/29)
Revision total knee arthroplasty	10.5% (2/19)	14.2% (2/14)

while showing relatively low osteoblast cytotoxicity [18,19]. Research into these alternatives is necessary, as no studies exist in the spinal surgery domain that study other intrawound antibiotics in humans.

Our study found no increase in the number of nonunions or wound complications when comparing both experimental cohorts with the control cohort. However, as the follow-up in the vancomycin cohort was shorter than the follow-up in the other cohorts, it is possible that the nonunion rate in the vancomycin group could further increase. Longer follow-up of the vancomycin patients will be necessary to draw definitive conclusions regarding the nonunion and the onset of antimicrobial resistance. No statistically significant increase in wound problems and culture negative seroma was seen in the vancomycin group.

Strengths of the current study include the large included patient cohort of patients with high risk of SSI (open, posterior instrumented surgery), as well as the fact that this study is one of the first to evaluate both povidone-iodine as well as vancomycin in a similar population in a single center, enabling comparison of the efficacy of both interventions. We also used the clear and unambiguous CDC criteria for SSI [1].

There are several limitations to our study. First, the study was not randomized, with associated risk of confounding. Because RCTs can potentially avoid these risks, they are often regarded as the optimal study design for therapeutic studies. Interestingly, there are two published RCTs that did not show a protective effect of vancomycin powder in spine surgery [20,21]. Unfortunately, both studies deviated from the most commonly applied method of decontamination of the entire wound with vancomycin. In one study, vancomycin was not applied to the instrumentation and bone [20], in the other study, the vancomycin was only applied when the muscular fascia had been closed [21]. One of the RCTs also did not report their criteria by which they defined SSI [20], and both studies included noninstrumented patients, which possibly underpowered the studies caused by the lower infection risk of these patients.

A second limitation of the current study is the fact that the study groups were noncontemporary. Because of this, it is possible that improved adherence to hygiene protocols and infection prevention measures other than intrawound vancomycin implemented over time may have caused the decrease in SSIs in the vancomycin group. One of these changes could be the change to new operating theatres, commissioned during the vancomycin cohort (Fig. 1). What makes this less likely is the fact that the introduction of the new theatres did not at all lead to SSI reductions in knee- and hip arthroplasty surgery at our institution (Table 3). Other preventive measures, like the use of laminar airflow, peri-operative IV antibiotic prophylaxis, *Staphylococcus aureus* nasal decontamination, chlorhexidine gluconate showering and hydrocolloid dressing were used in all three cohorts (and also in the THA/TKA patients).

Conclusion

Intrawound application of vancomycin powder was associated with a significant reduction in SSIs in instrumented spinal surgery, with a RR of 0.52 (95% CI 0.29−0.92) for deep and a RR of 0.31 (95% CI 0.12−0.81) for superficial SSIs. A 1.3g/L povidone-iodine solution lowered the incidence of superficial SSIs (RR 0.18, 95% CI 0.04−0.80) but not that of deep SSIs. Both intrawound treatments were not associated with an increased number of adverse events. No vancomycin-resistance or selection of gram-negative pathogens was observed in the vancomycin cohort.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2019.05.592.

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