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Negligible systemic uptake of suprafascial vancomycin powder following instrumented posterior spinal fusion – Preliminary results from a randomized clinical trial (VANCO Trial)

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Results from this sub-study have not been previously presented at any scientific meeting.

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Abstract

Background

Intrawound vancomycin powder is an emerging strategy to reduce surgical site infections (SSIs) in spine surgery. However, there are concerns relating to its safety profile and toxicity. Data on systemic uptake of suprafascially administered vancomycin powder following instrumented spinal fusion is lacking.

Objective

To study the systemic uptake and safety of suprafascially administered vancomycin powder in the early postoperative phase following open instrumented posterior spinal fusion.

Methods

This was a substudy of an ongoing randomized clinical trial. Eligible adult patients were randomized 1:1 to either receive suprafascial vancomycin powder before wound closure or not to receive vancomycin powder. Serum vancomycin levels were assessed on postoperative days 1 and 2, serum creatinine levels were measured pre- and postoperatively. Adverse events up to 6 weeks following surgery were recorded.

Results

Among 34 randomized patients (mean age 62 years, range 31-84 years; 18 [53%] women), 17 received vancomycin powder. No detectable serum vancomycin levels (> 4.0 mg/L) were found. Proportion of adverse events per patient in the vancomycin and control group, respectively, were 29.4% (5/17) vs. 11.8% (2/17) (OR 3.12; 95% CI, 0.52; 19.38; P = 0.398). No patient had nephrotoxicity or ototoxicity in either group.

Conclusion

Suprafascial vancomycin powder in open instrumented spinal fusion surgery is safe and results in negligible systemic uptake. Final results of the VANCO Trial need to be awaited for conclusive data on the efficacy of vancomycin for SSI prevention and its impact on wound healing.

Keywords: spinal fusion, spine surgery, surgical site infection, vancomycin powder, adverse drug reaction

Running Title: Suprafascial vancomycin powder in spine surgery

Introduction

Surgical site infections (SSIs) after open instrumented posterior spinal fusion procedures are feared complications and reported incidences range from 1 to 13%.[1,2] Most often the causative pathogens are gram-positive bacteria originating from the native skin flora.[2,3] Hence, the use of intrawound vancomycin powder to prevent SSIs in spine surgery has emerged as a common preventive measure. Many case series and systematic reviews have shown promising results with intrawound administration of vancomycin powder with significant reduction of the SSI rates.[4-9] However, current evidence on the prophylactic use of vancomycin powder in spine surgery is mainly based on retrospective case series, and well-designed prospective studies are lacking.[1,10] Therefore, the widespread and routine use of prophylactic intrawound vancomycin powder in spine surgery is controversial. One of the concerns is that the use of vancomycin powder may lead to an increase of SSIs caused by vancomycin-resistant organisms.[3,11-13] Another is related to nephrotoxicity and ototoxicity, well-known adverse events of systemic vancomycin treatment. A few studies have reported on serum vancomycin levels following vancomycin powder administration to deep subfascial tissue layers during orthopedic trauma and spine surgery.[14-16] In contrast, no data from prospective clinical trials exists regarding the safety profile and toxicity associated with the use of suprafascial vancomycin powder during instrumented spinal fusion surgery.

In this substudy of an ongoing randomized clinical trial (VANCO Trial) on the efficacy of suprafascially applied vancomycin powder for the prevention of SSI in open instrumented posterior spinal fusion, we investigated the systemic distribution and safety of suprafascially administered vancomycin powder.

Methods

Study design

This was an interim analysis (substudy) of the ongoing VANCO Trial, a multicenter, randomized controlled trial on the safety and efficacy of suprafascially applied vancomycin powder during open instrumented posterior spinal fusion initiated at our university hospital (ClinicalTrials.gov Identifier: BLINDED FOR REVIEW). The Trial was approved by the local ethics commission (ID BLINDED FOR REVIEW) and BLINDED FOR REVIEW (BLINDED FOR REVIEW Agency for Therapeutic Products; ref. no. BLINDED FOR REVIEW). The trial is currently being performed at four sites in BLINDED FOR REVIEW. For this substudy all patients were enrolled between November 2019 and November 2020 at the trial initiating site.

Study interventions

Eligible patients are randomized 1:1, and randomization takes place intraoperatively shortly before wound closure. Allocation of patients is done centrally via a password protected database, stratified to the following criteria: trial site, vertebral levels fused (1 vs. ≥ 2 levels), insulin-dependent diabetes, and body mass index (<30 vs. ≥30 kg/m^2). In order to minimize bias, group allocation is communicated to the surgical team only shortly before wound closure. In the vancomycin group patients receive 1 g of vancomycin powder as a standard dose, which is applied suprafascially above the closed muscle fascia. As previously reported, risk for postoperative subfascial seroma formation, adverse effects on bone healing and neural elements, as well as washout by subfascial drains were thought to be better averted by suprafascial vancomycin powder.[9] For skin incisions >20 cm, 2 g of vancomycin powder are used. Patients randomized to the control group do not receive intrawound vancomycin powder. Patients are blinded to group allocation. All other pre-, intra- and postoperative procedures are conducted according to standard practice of the study site. Measurements of serum vancomycin levels were terminated after inclusion of the first 34 patients as discussed in a scientific consensus meeting with our infectious disease advisory board.

Patient population

Inclusion criteria for the VANCO Trial are age 18 years or older and need for open instrumented posterior spinal fusion. Exclusion criteria are concurrent systemic infectious disease, solely minimally-invasive spine surgery, prior spine surgery at the index level within the last 90 days, need for postoperative radiation therapy, known allergy for vancomycin, preexisting inner ear disorder, pregnancy, and inability to give informed consent for trial participation. Early reoperations and postoperative radiation were defined as exclusion criteria since these patients seem to be more susceptible to wound healing disturbances or even deep wound dehiscences with secondary SSI. We hypothesized, that intrawound vancomycin powder would not be able to sufficiently mitigate this risk.

Standard perioperative operating procedures

All patients routinely received standard antiseptic surgical skin preparation with povidone-iodine 7.5% (Betadine®) scrub and standard sterile draping. Preoperatively patients were given cefuroxime 1.5 g as intravenous prophylaxis, or 600 mg of clindamycin as an alternative in cases

of suspected or confirmed allergy to cephalosporins. The intravenous antibiotic prophylaxis was repeated if the duration of surgery exceeded three hours and was discontinued postoperatively.
All fusion procedures within this study were performed in an open fashion using a rigid screw-rod-system with or without intervertebral implants for lumbar interbody fusion. A subfascial suction drain was routinely placed. The wound was closed in a standard layered fashion.

Data collection

Preoperative data collection included demographic and medical data, such as preoperative serum creatinine levels (1-3 days prior to surgery) and glomerular filtration rate (GFR), and self-assessment of hearing. Surgical data included information on the pathology and main indication for surgery, location of spinal fusion and number of levels fused. Postoperative data collection incorporated clinical assessment of wound healing, serum vancomycin levels on postoperative day (POD) 1 and 2, postoperative serum creatinine levels before hospital discharge, and postoperative self-assessment of hearing.

Outcome assessments

The primary outcome measure were serum vancomycin levels on POD 1 and 2. Secondary outcomes were postoperative serum creatinine levels before discharge, and the rate of both local and systemic vancomycin related adverse events up to 6 weeks after surgery. At this point, a physician blinded to group allocation undertook a clinical examination. In addition, patients were asked postoperatively and at every follow-up about any new impairment of their hearing ability since the surgery.

Statistical analysis

Descriptive data are presented as mean ± standard deviation or frequencies and percentages for continuous and categorical variables, respectively. Categorical outcomes (risk of complications) were compared using Chi-square (χ^2) or Fisher exact tests for differences in proportions, as appropriate, and further displayed with OR and 95% confidence interval obtained from a logistic model. Postoperative nephrotoxicity was defined as a 50% increase in the serum creatinine concentration from that at the baseline. The therapeutic reference range for serum vancomycin levels at our university hospital laboratory is defined as 10-15 mg/L, or 15-20 mg/L for specific indications. Very low or undetectable serum vancomycin levels are indicated as <4.0 mg/L, which

is our laboratory's lower level of quantification. The statistical analysis was performed using Stata, StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.

Results

Patient flow through the trial is presented in Figure 1. Of the first 34 patients (mean age 62 years, range 31-84 years; 18 [53%] women) enrolled in the VANCO Trail, 17 patients were randomized to the treatment arm, and received intrawound vancomycin powder. Sixteen of these patients received 1 g, and one patient received 2 g of vancomycin powder (skin incision > 20 cm) administered suprafascially before wound closure. Baseline characteristics, type of pathology, location of surgery, and number of levels fused for both groups are shown in Table 1.

All of the patients in the treatment group had serum vancomycin levels below the limit of quantification (<4.0 mg/L) on POD 1 (range: 16-25 hours postoperatively) and POD 2 (range: 41-44 hours). Serum vancomycin levels were missing in three patients (for one patient on POD 1 and 2, for one patient on POD 1, and for one patient on POD 2). No patient experienced postoperative nephrotoxicity. Two patients in the treatment arm showed increases in postoperative serum creatinine levels (+2% and +26%), compared to eight patients in the control group (range: +4% to +29%) (Figure 2).

The proportion of patients with at least one adverse event in the vancomycin and control group, respectively, were 29.4% (5/17) vs. 11.8% (2/17) (OR 3.12; 95% CI, 0.52; 19.38; $P = 0.398$) (Table 2). No cases of ototoxicity were recorded. Before hospital discharge two patients in the vancomycin group who had lumbar fusions for a degenerative condition had persistent serous discharge from the wound but no clinical evidence of a SSI. A third patient in the vancomycin group developed a large wound seroma with fascial dehiscence at the cervicothoracic junction four weeks following a T1-2 decompression and fusion. The seroma was drained and revealed no bacterial growth. One patient in the control group suffered a deep SSI with fascial dehiscence three weeks following posterior laminectomy and instrumented C3-T2 fusion. Cultures from the wound showed evidence of coagulase-negative staphylococci. Following targeted antibiotic therapy and vacuum-assisted closure dressings, the wound was finally covered four weeks after the index surgery with a lower trapezius island myocutaneous flap.

Discussion

Key Results

We present preliminary results on the systemic effect of suprafascial vancomycin powder in open instrumented posterior spinal fusion from a randomized clinical trial. All patients with topical vancomycin administration had vancomycin serum levels below the limit of quantification one and two days after the operation indicating there was no measurable systemic uptake of the antibiotic. In keeping with these results, we found no evidence for vancomycin-induced nephrotoxicity nor for ototoxicity. We found no statistical significant difference in adverse events between both groups.

Vancomycin-associated Adverse Drug Reactions

The safety and risk profile of intravenous vancomycin is well described. Known vancomycin-associated adverse reactions, when administered by an intravenous route, include thrombophlebitis, red man syndrome, ototoxicity, and nephrotoxicity.[17] A major advantage intrawound vancomycin powder is the prospect of negligible systemic toxicity. However, despite its widespread use and many retrospective studies, there is a paucity of prospective scientific reports on the systemic uptake, safety profile and toxicity of topical vancomycin powder in spine surgery. As mentioned earlier, the incidence of drug-related complications attributed to the use of vancomycin powder has been reported to be as low as 0.3% in a recent systematic review of mainly retrospective studies.[18] In this review, a total of 6701 patients, who underwent lumbar spine surgery, received prophylactic intrawound vancomycin powder. Of the total of 23 drug related complications, 19 cases of wound seromas, two cases of transient hearing loss, one case of nephropathy, and one case of supratherapeutic serum vancomycin levels were reported. In another review of 1512 consecutive spinal surgical cases using prophylactic intrawound subfascial vancomycin powder, only one case of otherwise unexplained postoperative renal failure was found, being the only drug-related complication (0.07%).[19] Further retrospective cohort studies reported no adverse events related to the use of vancomycin powder in spine surgery.[4,9] In our cohort three patients developed wound healing disorders. Vancomycin-associated spontaneous cutaneous adverse drug reactions with suspected immune-mediated delayed hypersensitivity reactions have been reported with intravenous administration.[20] Possibly, wound discharge and seroma formation might represent allergic or inflammatory reactions to local vancomycin powder.[9,21] As the VANCO Trial includes more patients, we hope to better understand the local effects of suprafascial vancomycin powder on wound healing.

While the reporting of low complication rates may promote a routine use of prophylactic

intrawound vancomycin powder, the data should be interpreted with caution, since a recall bias is a relevant limitation of retrospective studies. However, the safety of vancomycin powder in spine surgery is underlined by the few existing prospective studies in which no adverse effects related to vancomycin powder were found.[7,15,22,23]

Intrawound vancomycin powder and serum vancomycin levels

The extremely low incidence of systemic complications from the use of vancomycin powder is in line with our findings of undetectable serum vancomycin levels. Evidently, vancomycin powder is only poorly absorbed from the wound, which has previously been confirmed by other authors. Sweet et al. found undetectable serum vancomycin levels in 80% (minimum sensitivity of 0.6 g/L) and very low levels (mean of 1.6 g/L, range 0.7-5.9 g/L) in 20% of patients on postoperative day 1 in 178 posterior thoracolumbar fusions in which 2 g vancomycin powder was applied to the sub- and suprafascial wound.[4] In addition, in this study, vancomycin drug levels in surgical drainage fluid peaked directly after surgery with mean levels of 1475 g/L and dropped to a mean of 128 g/L on day 3. Supratherapeutic drain levels that exceeded the mean inhibitory concentration (MIC) for common pathogens by more than 50-fold were also measured in a cohort of 25 pediatric patients who received 1 g of intrawound vancomycin powder during spinal deformity surgery.[14] Mean serum vancomycin levels immediately after surgery were 2.5 g/L, and no systemic adverse effects were observed. In a prospective study by Murphy and colleagues 52 patients undergoing instrumented spinal fusion were allocated to two groups with 24 patients receiving 1g, and 28 patients receiving 2 g of subfascial vancomycin powder. Only one patient in the 1 g group (4.4 g/L at 12 hours), and four patients in the 2 g group reached detectable serum vancomycin levels with peak levels up to 7.8 g/L (with 2 g of vancomycin powder) at 6-12 hours after surgery.[15] No adverse effects were detected. Similar results were found in orthopedic trauma surgery. A recent prospective study reported undetectable serum vancomycin levels in 58 patients with tibial plateau and pilon fractures using 1 g of intrawound vancomycin powder, and no cases of vancomycin induced nephrotoxicity were recorded.[24]

This existing evidence on the use of intrawound vancomycin powder suggests the creation of a local environment with very high wound vancomycin levels that largely exceed the MIC target AUC_{24} levels to kill most gram-positive bacteria during the first days after surgery, while serum levels remain near undetectable. Consequently, reported rates of local and systemic adverse events associated with vancomycin powder are very low. Furthermore, as Sweet et al. have previously

argued, poor systemic absorption of topical vancomycin should lead to a lower risk for developing remote vancomycin-resistant bacterial infections.[4] This hypothesis has been supported by a recent meta-analysis of nearly 20'000 patients treated with intrawound vancomycin powder during spine surgery with no increase in the incidence of vancomycin-resistant infections.[8]

Limitations

The present study has several limitations. First, obviously the number of trial patients included in this substudy is low, with merely 17 patients randomized to the treatment arm. However, in accordance with our infectious disease advisory board involved in this ongoing trial, it was decided to discontinue further measurements of postoperative serum vancomycin levels, since no evidence of systemic uptake was found. Second, the assessment of vancomycin-associated ototoxicity was based on elicited, patient reported postoperative hearing impairment. Due to its low incidence even with systemic vancomycin treatment, pre- and postoperative audiogram monitoring did not seem justified. Third, while other studies on the use of intrawound vancomycin powder monitored very early serum vancomycin levels within the first hours after surgery,[14,15,24] the levels in our study were analyzed on POD 1 and 2. Also, our laboratory's level of quantification of serum vancomycin levels was 4.0 g/L. We were thus unable to detect very early postoperative low serum vancomycin concentrations.

Conclusion

Prophylactic use of intrawound vancomycin powder placed in the suprafascial plane for the prevention of SSIs in open instrumented posterior spinal fusion surgery has so far shown an excellent safety profile with negligible systemic uptake and no systemic adverse events. Intrawound vancomycin powder is a safe and cost-effective option to potentially decrease the risk for SSIs. However, the final results of the VANCO Trail need to be awaited to conclude on the efficacy of suprafascial vancomycin powder of preventing SSIs in open instrumented spinal fusion and its impact on local wound healing as well as on the pathogen profile in cases with SSIs.

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Figures

Figure 1: Flow diagram of trial participants

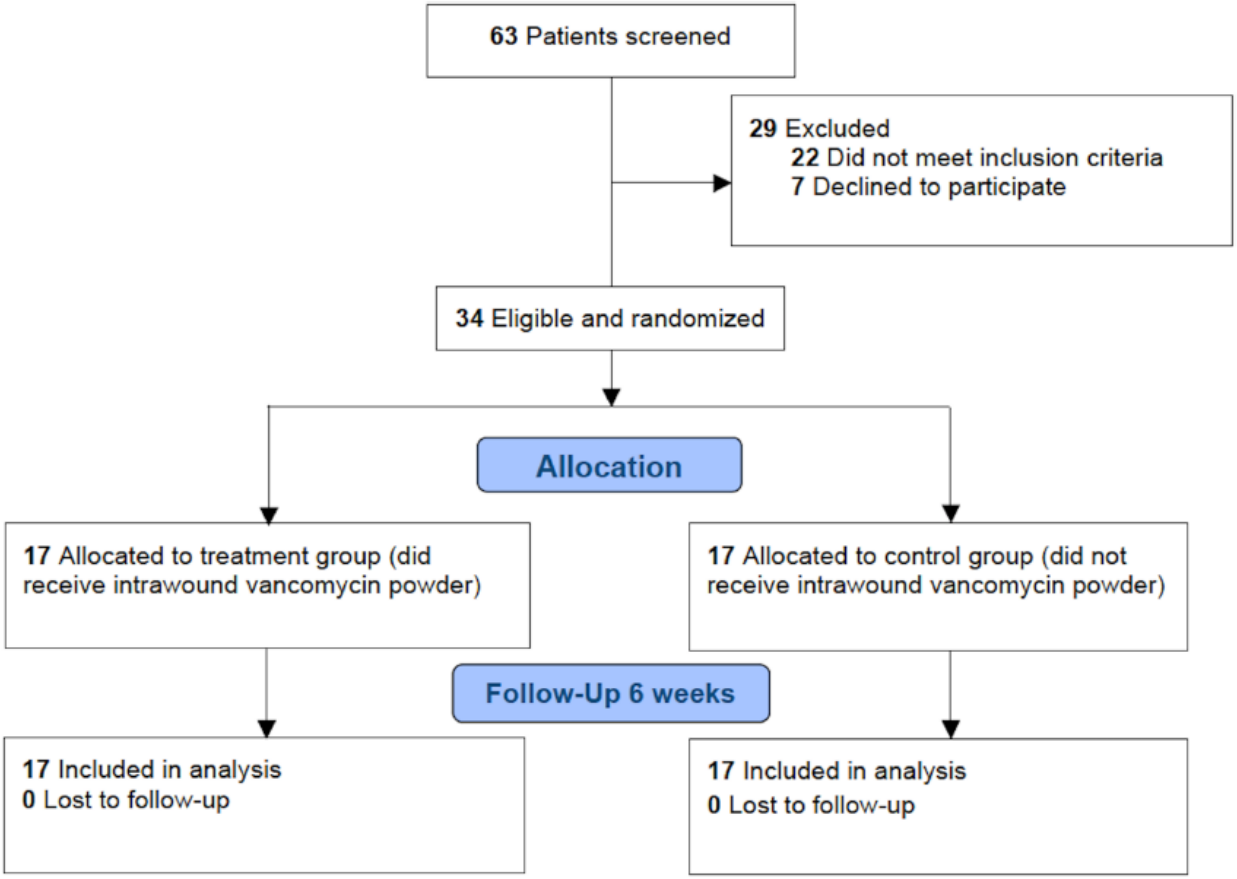
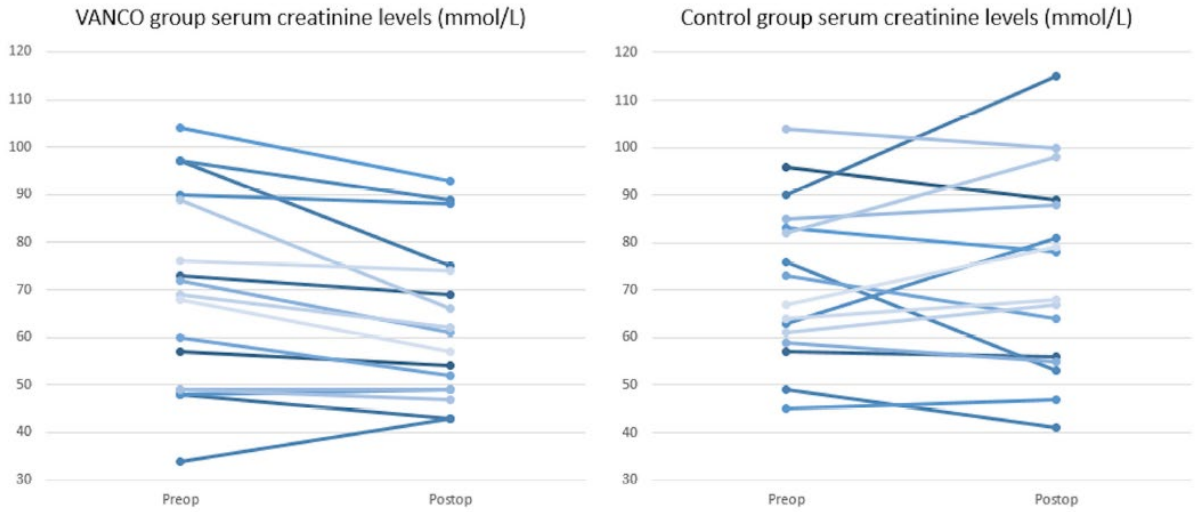


Figure 2: Graphs representing pre- and postoperative serum creatinine levels of patients in the vancomycin and control group.



411 **Table 1.** Baseline patient characteristics

Characteristics	Treatment group (n = 17)	Control group (n = 17)
Age, mean (SD)	63.5 (15.9)	60.5 (17.9)
Sex, No. (%)		
Female	11 (64.7)	7 (41.2)
Male	6 (35.3)	10 (58.8)
ASA physical status class, No. (%)		
I (healthy)	0	1 (5.9)
II (mild systemic disease)	5 (29.4)	7 (43.8)
III (severe systemic disease)	9 (52.9)	8 (47.1)
IV (severe systemic disease with constant threat to life)	3 (17.6)	1 (5.9)
Diabetes, No. (%)	6 (35.3)	2 (11.8)
Tobacco use, No. (%)	4 (23.5)	3 (17.6)
BMI kg/m^2, mean (SD)	28.4 (4.5)	25.9 (4.7)
History of cancer, No. (%)	2 (11.8)	2 (11.8)
Type of pathology, No. (%)		
Degenerative	14 (82.4)	10 (58.8)
Trauma	0	3 (17.6)
Reoperation	2 (11.8)	3 (17.6)
Isthmic spondylolisthesis	1 (5.9)	1 (5.9)
Location, No. (%)		
Cervical	0	0
Cervicothoracic	5 (29.4)	3 (17.6)
Thoracic	1 (5.9)	0
Thoracolumbar or thoracolumbosacral	1 (5.9)	1 (5.9)
Lumbar or lubosacral	10 (58.8)	13 (76.5)
No. of levels fused, No. (%)		
1	10 (58.8)	10 (58.8)
2 - 3	3 (17.6)	4 (23.5)
4 - 5	2 (11.8)	2 (11.8)
> 5	2 (11.8)	1 (5.9)

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413 ASA American Society of Anesthesiologists physical status classification, BMI body mass index, SD
414 standard deviation

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Table 2. Adverse events related to surgery or intervention by group allocation

Adverse events	No. (%)	
	Treatment group (n = 17)	**Control group (n = 17)**
Patients with complications[1]	5 (29.4)	2 (23.5)
Reoperation	1 (5.9)	2 (11.8)
Reason for reoperation		
SSI	0	1 (5.9)
Revision of hardware	1 (5.9)	1 (5.9)
Wound healing disorder	3 (17.6)	1 (5.9)
Serous discharge from wound	2 (11.8)	0
Seroma	1 (5.9)	0
SSI	0	1 (5.9)
Ototoxicity	0	0
Nephrotoxicity	0	0
Urinary tract infection	0	1 (5.9)
Pulmonary embolism	1 (5.9)	0

SSI surgical site infection

[1] Patients may have had more than 1 complication, totals (patients with complications) may be less than sum of categories.