

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

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18

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32 **Abstract**

33 *Background*

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

38 *Objective*

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

41 *Methods*

42 This was a substudy of an ongoing randomized clinical trial. Eligible adult patients were
43 randomized 1:1 to either receive suprafascial vancomycin powder before wound closure or not to
44 receive vancomycin powder. Serum vancomycin levels were assessed on postoperative days 1 and
45 2, serum creatinine levels were measured pre- and postoperatively. Adverse events up to 6 weeks
46 following surgery were recorded.

47 *Results*

48 Among 34 randomized patients (mean age 62 years, range 31-84 years; 18 [53%] women), 17
49 received vancomycin powder. No detectable serum vancomycin levels (> 4.0 mg/L) were found.
50 Proportion of adverse events per patient in the vancomycin and control group, respectively, were
51 29.4% (5/17) vs. 11.8% (2/17) (OR 3.12; 95% CI, 0.52; 19.38; $P = 0.398$). No patient had
52 nephrotoxicity or ototoxicity in either group.

53 *Conclusion*

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

57
58 **Keywords:** spinal fusion, spine surgery, surgical site infection, vancomycin powder, adverse drug
59 reaction

60 **Running Title:** Suprafascial vancomycin powder in spine surgery

61

62 **Introduction**

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

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

83

84 **Methods**

85 *Study design*

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

94

95 *Study interventions*

96 Eligible patients are randomized 1:1, and randomization takes place intraoperatively shortly before
97 wound closure. Allocation of patients is done centrally via a password protected database, stratified
98 to the following criteria: trial site, vertebral levels fused (1 vs. ≥ 2 levels), insulin-dependent
99 diabetes, and body mass index (<30 vs. ≥ 30 kg/m²). In order to minimize bias, group allocation is
100 communicated to the surgical team only shortly before wound closure. In the vancomycin group
101 patients receive 1 g of vancomycin powder as a standard dose, which is applied suprafascially
102 above the closed muscle fascia. As previously reported, risk for postoperative subfascial seroma
103 formation, adverse effects on bone healing and neural elements, as well as washout by subfascial
104 drains were thought to be better averted by suprafascial vancomycin powder.⁹ For skin incisions
105 >20 cm, 2 g of vancomycin powder are used. Patients randomized to the control group do not
106 receive intrawound vancomycin powder. Patients are blinded to group allocation. All other pre-,
107 intra- and postoperative procedures are conducted according to standard practice of the study site.
108 Measurements of serum vancomycin levels were terminated after inclusion of the first 34 patients
109 as discussed in a scientific consensus meeting with our infectious disease advisory board.

110

111 *Patient population*

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

121

122 *Standard perioperative operating procedures*

123 All patients routinely received standard antiseptic surgical skin preparation with povidone-iodine
124 7.5% (Betadine[®]) scrub and standard sterile draping. Preoperatively patients were given
125 cefuroxime 1.5 g as intravenous prophylaxis, or 600 mg of clindamycin as an alternative in cases

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

131

132 *Data collection*

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

140

141 *Outcome assessments*

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

148

149 *Statistical analysis*

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

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

160

161 **Results**

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

168 All of the patients in the treatment group had serum vancomycin levels below the limit of
169 quantification (<4.0 mg/L) on POD 1 (range: 16-25 hours postoperatively) and POD 2 (range: 41-
170 44 hours). Serum vancomycin levels were missing in three patients (for one patient on POD 1 and
171 2, for one patient on POD 1, and for one patient on POD 2). No patient experienced postoperative
172 nephrotoxicity. Two patients in the treatment arm showed increases in postoperative serum
173 creatinine levels (+2% and +26%), compared to eight patients in the control group (range: +4% to
174 +29%) (Figure 2).

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

187

188 **Discussion**

189 Key Results

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

197

198 *Vancomycin-associated Adverse Drug Reactions*

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

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

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

226

227 *Intrawound vancomycin powder and serum vancomycin levels*

228 The extremely low incidence of systemic complications from the use of vancomycin powder is in
229 line with our findings of undetectable serum vancomycin levels. Evidently, vancomycin powder is
230 only poorly absorbed from the wound, which has previously been confirmed by other authors.
231 Sweet et al. found undetectable serum vancomycin levels in 80% (minimum sensitivity of 0.6 g/L)
232 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
233 in 178 posterior thoracolumbar fusions in which 2 g vancomycin powder was applied to the sub-
234 and suprafascial wound.⁴ In addition, in this study, vancomycin drug levels in surgical drainage
235 fluid peaked directly after surgery with mean levels of 1475 g/L and dropped to a mean of 128 g/L
236 on day 3. Supratherapeutic drain levels that exceeded the mean inhibitory concentration (MIC) for
237 common pathogens by more than 50-fold were also measured in a cohort of 25 pediatric patients
238 who received 1 g of intrawound vancomycin powder during spinal deformity surgery.¹⁴ Mean
239 serum vancomycin levels immediately after surgery were 2.5 g/L, and no systemic adverse effects
240 were observed. In a prospective study by Murphy and colleagues 52 patients undergoing
241 instrumented spinal fusion were allocated to two groups with 24 patients receiving 1g, and 28
242 patients receiving 2 g of subfascial vancomycin powder. Only one patient in the 1 g group (4.4 g/L
243 at 12 hours), and four patients in the 2 g group reached detectable serum vancomycin levels with
244 peak levels up to 7.8 g/L (with 2 g of vancomycin powder) at 6-12 hours after surgery.¹⁵ No adverse
245 effects were detected. Similar results were found in orthopedic trauma surgery. A recent
246 prospective study reported undetectable serum vancomycin levels in 58 patients with tibial plateau
247 and pilon fractures using 1 g of intrawound vancomycin powder, and no cases of vancomycin
248 induced nephrotoxicity were recorded.²⁴

249 This existing evidence on the use of intrawound vancomycin powder suggests the creation of a
250 local environment with very high wound vancomycin levels that largely exceed the MIC target
251 AUC₂₄ levels to kill most gram-positive bacteria during the first days after surgery, while serum
252 levels remain near undetectable. Consequently, reported rates of local and systemic adverse events
253 associated with vancomycin powder are very low. Furthermore, as Sweet et al. have previously

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

258

259 *Limitations*

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

272

273 **Conclusion**

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

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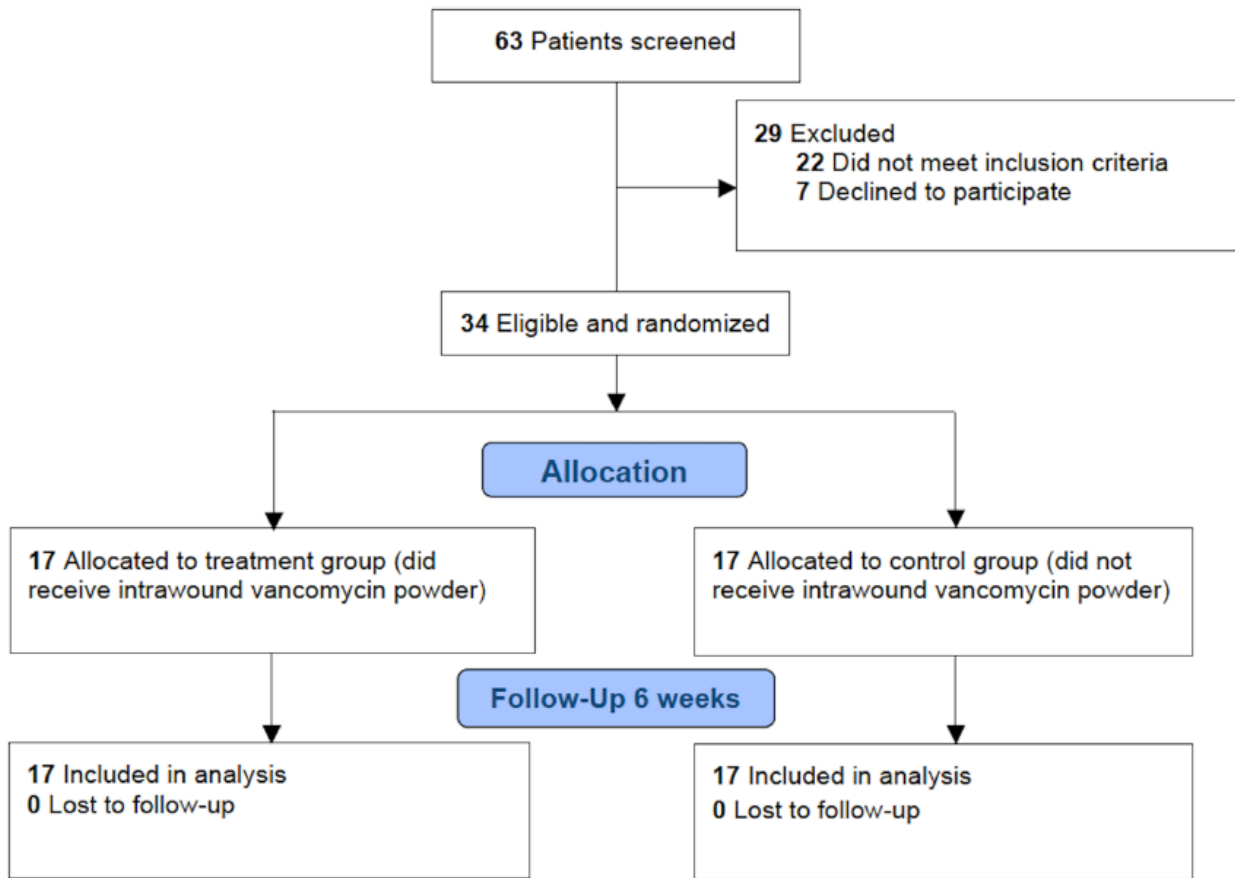
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404 **Figures**

405 Figure 1: Flow diagram of trial participants

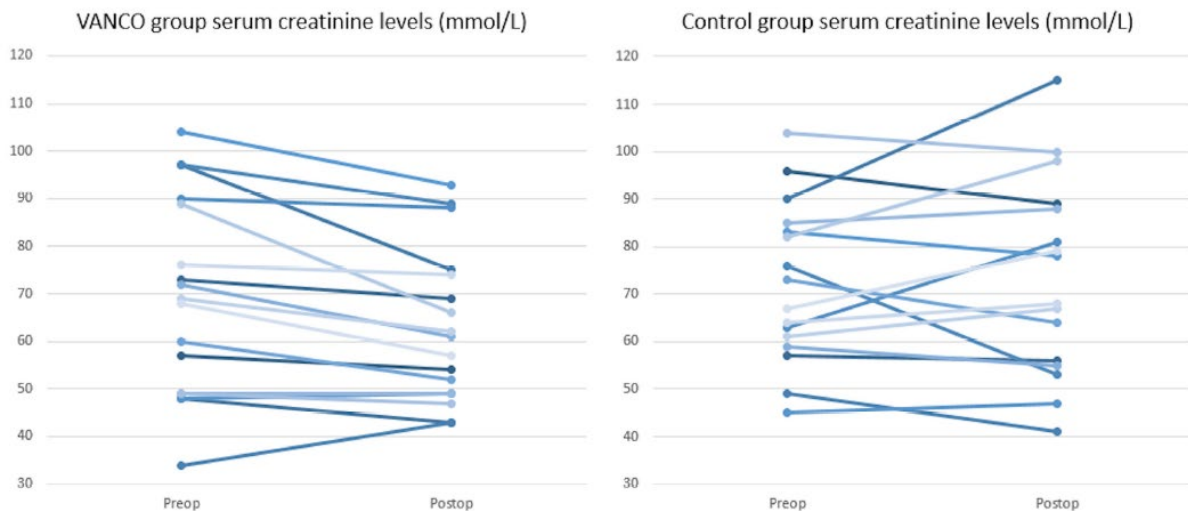


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408 Figure 2: Graphs representing pre- and postoperative serum creatinine levels of patients in the

409 vancomycin and control group.



410

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)

412

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

415

416 **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)
<i>Reason for reoperation</i>		
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

417

418 SSI surgical site infection

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