

# Effectiveness of Topical Vancomycin in the Prevention of Spinal Surgical Site Infections: A Retrospective Cohort Study

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## Research Article

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# Abstract

## Background

The risk of surgical site infections (SSIs), particularly methicillin-resistant staphylococcus aureus (MRSA) SSIs, post spinal surgeries is one of the most daunting experiences to patients and surgeons. In some practices, vancomycin powder is applied directly on the wound before skin closure to minimize the risk of SSIs; however, this practice is not supported by well-established evidence. This study sought to assess the effectiveness of topical (i.e. intra-wound) vancomycin in minimizing the risk of SSIs in patients who underwent spinal surgeries at the Kingdom Hospital (a private Saudi hospital).

## Methods

A retrospective cohort study was conducted using the hospital database. Patients who underwent spinal surgeries from the period of 09/2013 to 09/2019 were included and followed up to 30 days (surgeries without implantation) or 90 days (with implantation). The odds ratio (OR) of the primary outcome between vancomycin users vs. non-users was estimated using logistic regression adjusting for the measured confounders. A sensitivity analysis was conducted using propensity score analysis (inverse probability of treatment weighting (IPTW) with stabilized weights) to control for confounding by indication. All study analyses were completed using RStudio Version 1.2.5033.

## Results

We included 81 vancomycin users vs. 375 non-users with 28 infections. The adjusted OR of SSIs between the two groups was 0.40 (95% confidence interval [CI] 0.11 to 1.34). The result of the propensity score analysis was consistent (OR: 0.97 [95% CI 0.35 to 2.68]).

## Conclusion

We could not find a lower association of SSIs with intra-wound vancomycin in patients who underwent spinal surgeries. Further studies are needed to assess benefits of using topical vancomycin for this indication vs. the risk of antimicrobial resistance.

## Background

Surgical site infections (SSIs) are the third most common complication among patients who underwent spinal surgeries with an overall incidence of 3.1% (the incidence is up to 13.0% in the highest risk group) [1–3]. SSIs are defined as infections occurring after 30 days from the operative procedure or up to 90 days in complicated deep incisions requiring implants [4]. They are burdensome complications and associated with a high risk of morbidity (especially readmission), mortality and economic loss [5]. In the United States, the direct and indirect health cost of post-spinal surgery SSIs is up to 10 billion dollars with a mortality rate of 8,000 deaths per year [6]. The risk is the highest among patients with thoracic spinal procedures (3.7%), followed by the cervical and lumbar procedures (3.4 % and 2.7 %), respectively [1]. The

benefits of some preventative measures against SSIs using prophylactic antibiotic regimens (with cefazolin as a fixed component) have been outweighed by the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) [7–12]. This led to the off-label use of topical vancomycin (i.e. intra-wound) in some practices [13–41].

The off-label topical application of 1-2g vancomycin powder from the injectable dosage forms for the prevention of post-spinal surgery SSIs has been controversial [13–41]. The published studies on the effect of this application in the prevention of post-spinal surgery SSIs have shown mixed results [13–41]. Additionally, the design of these studies was subjected to several methodological limitations (e.g. the absence of a control group, the suboptimal choice of the control group, the suboptimal definition of the outcome, the suboptimal adjustment of potential measured confounders, ignoring the impact of some known effect modifiers, etc.). The aim of this study was to assess the effectiveness of topical vancomycin in the prevention of post-spinal surgery SSIs taking into consideration the aforementioned design limitations in a Saudi population.

## Methods

### Source of data

This retrospective cohort study was conducted using the database of a private hospital (the Kingdom Hospital) in Riyadh, Saudi Arabia. Data from the routine clinical care are added to the hospital's electronic health records. Diseases are coded using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Patient socio-demographic details, surgery type, relevant lab investigations (including culture sensitivity results), re-admission, follow-up periods and patient outcome were collected through a direct access to the electronic health records. Original patient medical charts were also accessed to collect missing values of the aforementioned variables and to collect data about additional covariates (past medical history, operation time, topical drug/intra-operative systemic drug exposure, and vital signs).

### Study cohort

Patients who underwent spinal surgeries from the period of 09-2013 to 09-2019 were included and followed up to 30 days (patients without implantation) or 90 days (patients with implantation). This follow-up period is reflective of the maximum follow-up period stated in the definition of post-spinal surgery SSIs in the "Introduction" section. All types of spinal surgeries were included in the study (i.e. lumbar, thoracic, thoracolumbar, and cervical) using the anterior or the posterior approach. All patients were given a prophylactic systemic cefazolin injection within 60 minutes before the scheduled surgeries.

### Study exposure and outcome

The included patients in this study were split into two exposure groups: incident vancomycin users (test group) and vancomycin non-users (control group). The cohort entry date was defined as the date of the spinal surgery. The outcome was the first SSI observed in the follow-up period.

# Confounders

The analysis of the study outcome was adjusted for the following potentially confounding variables: age, sex, body mass index (BMI), type of spinal surgery, smoking status, diabetes mellitus, kidney functions, hypertension, history of spinal surgeries, history of antibiotic use within 90 days before cohort entry date, prolonged operation time (an operation lasting 100 minutes or more), surgical approach (anterior vs. posterior), implantation, use of disinfectants (alcohol, betadine, chlorhexidine), topical gentamicin solution for irrigation (not all patients were given gentamicin), pre- and post-operative inflammatory/infection markers such as white blood cell counts and neutrophil counts. These potential confounders were reported in the literature as potential risks for the outcome of the study with an assumption that none of them is an instrumental variable [1, 44–56].

## Statistical analysis

The primary hypothesis of the study was that topical vancomycin use is superior to non-vancomycin use in the prevention of post-spinal surgery SSIs. This hypothesis was tested using a logistic regression model adjusting for the measured confounders. The observed number of the primary outcome events was low; therefore, the odds ratio (OR) estimated from the model would provide a close approximation of the relative risk.

There is a tendency at the hospital to prescribe topical vancomycin for patients who are at a high risk of SSIs post-spinal surgeries. Thus, a sensitivity analysis was conducted using propensity score analysis to take into account the possible risk of confounding by indication [57–60]. In the first step, propensity scores (the probability of assignment to vancomycin group) for the included patients were estimated using a logistic regression model incorporating all study measured confounders. Then, a propensity score analysis was conducted using inverse probability of treatment weighting (IPTW) with stabilized weights. The balance check in the new “pseudo-population” was based on the absolute standardized difference (SMD) (a balance was achieved if SMD is < 10%). All statistical analyses were conducted using RStudio Version 1.2.5033.

## Results

We included 456 patients who were either incident vancomycin users (n = 81) or non-users (n = 375) (Table 1). The dosage range of vancomycin was 0.5 to 2g and the majority of patients were given 1g (61 of 81 [75%]). Most patients underwent lumbar surgeries (343 of 456 [75%]), most surgeries had a posterior approach (425 of 456 [93%]), and more than two-third of patients were given prophylactic gentamicin solution for irrigation (349 of 456 [77%]).

Table 1  
Baseline characteristics of the study groups

Baseline characteristics	Vancomycin users N = 81	Vancomycin non-users N = 375	Difference (p-value)*
Age (years)	50	45	0.06
Median	27	22	
IQR			
Sex no. (%)	47 (58.0)	249 (66.4)	0.19
Male	34 (42.0)	126 (33.6)	
Female			
BMI (kg/m <sup>2</sup> )	29.7	29.4	0.52
Median	8.4	7.2	
IQR			
Type of surgery no. (%)	58 (72.0)	285 (76.0)	< 0.01
Lumbar	5 (6.0)	5 (1.0)	
Thoracic	15 (18.0)	30 (8.0)	
Thoracolumbar	3 (4.0)	55 (15.0)	
Cervical			
Smoking history no. (%)	60 (74.0)	232 (62.0)	0.12
Never smokers	19 (23.0)	125 (33.3)	
Current smokers	2 (3.0)	18 (5.0)	
Former smokers			
Diabetes mellitus no. (%)	20 (25.0)	64 (17.0)	0.14
Renal functions no. (%)	79 (98.0)	371 (99.0)	0.28
Normal	2 (2.0)	4 (1.0)	
Abnormal			
Hypertension no. (%)	29 (36.0)	98 (26.0)	0.10
History of spinal infection no. (%)	4 (5.0)	3 (1.0)	0.02
History of spinal surgeries no. (%)	19 (23.0)	54 (14.0)	0.06

Baseline characteristics	Vancomycin users N = 81	Vancomycin non-users N = 375	Difference (p-value)*
History of antibiotic use within 90 days before index date no. (%)	13 (16.0)	28 (8.0)	0.03
Prolonged operation time no. (%)	71 (88.0)	29 (8.0)	< 0.01
Surgical approach no. (%)	0 (0.0)	31 (8.0)	< 0.01
Anterior	81 (100.0)	344 (92.0)	
Posterior			
Implant no. (%)	72 (89.0)	184 (49.0)	< 0.01
Alcohol as disinfectant no. (%)	70 (86.0)	303 (81.0)	0.30
Prophylactic gentamicin solution for irrigation no. (%)	68 (84.0)	281 (75.0)	0.11
Pre-operative white blood cell counts (in 10 <sup>3</sup> /μl)	7.5	8.2	0.08
Median	3.8	3.1	
IQR			
Pre-operative neutrophil counts (%)	54.7	57.4	0.13
Median	13.9	13.9	
IQR			

A total of 28 cases of post spinal surgery SSIs were identified in vancomycin user vs. non-user groups (8 of 81 [9.9%] vs. 20 of 375 [5.3%], respectively). Out of 28 infections, 16 (57%) were considered deep and 12 (43%) were superficial. Some patients were infected by more than 1 isolated pathogens which explains the higher number of the total isolated microbes compared with the number of SSI cases (36 vs. 28 respectively), (Table 2). The microbiological analysis revealed that 50 % (14/28) of these SSIs were caused by Staphylococcus species (4 vs. 10 in vancomycin user and non-user groups, respectively). The other 50% were caused mostly by Gram negative bacteria such as Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli isolates (Table 3). The odds of SSIs in the vancomycin group was comparable to the odds in the non-exposure group: OR = 0.40 (95% confidence interval [CI] 0.11 to 1.34). The results of propensity score estimation showed a clear evidence of confounding by indication (i.e. a large proportion of the patients in the non-exposure group had a propensity of zero) as shown in Fig. 1, which also prevented trimming of the extreme values. The balance was achieved in 50% of the variables in the pseudo-population. The result of the IPTW analysis was consistent with the results of the first analysis; however, the direction of the point estimate shifted to the null value: OR = 0.97 (95%CI 0.35 to 2.68).

Table 2  
Microbiological Analysis in Post-Spinal Surgery SSIs:

Infection Type (superficial or deep)	Isolated microbe
deep	M. Tb
deep	MSSA
deep	K. pneumoniae
deep	MSSA
superficial	Pseudomonas aeruginosa
deep	E.coli-ESBL*
deep	M. Tb
deep	Pseudomonas aeruginosa
deep	MSSA
superficial	Staph epidirmidis
superficial	Staphylococcus hominis, E.coli
superficial	MSSA
deep	Enterobacter cloacea-MDR**, Morganella Morgani, Pseudomonas aeruginosa, Klebsiella pneumoniae-ESBL
deep	K. pneumoniae-ESBL/ Acinetobacter Baumannii
deep	Morganella Morgannii, Pseudomonas aeruginosa
deep	MRSA
superficial	CoNS, K. pneumoniae-ESBL*, E.coli-ESBL*
superficial	MSSA
superficial	E. coli
deep	MRSA
deep	MRSA
superficial	MSSA
superficial	CoNS
superficial	MSSA
<i>*ESBL: extended-spectrum beta lactamase</i>	
<i>**MDR: multi-drug resistant</i>	

Infection Type (superficial or deep)	Isolated microbe
deep	Pseudomonas aeruginosa
deep	MRSA
superficial	Pseudomonas aeruginosa
superficial	MSSA
<i>*ESBL: extended-spectrum beta lactamase</i>	
<i>**MDR: multi-drug resistant</i>	

Table 3  
Isolated microbes in infected Vancomycin users and Vancomycin non-users:

Isolated microbe	Total number of isolates N = 36	Vancomycin users N = 11	Vancomycin non-users N = 25
Methicillin Sensitive Staphylococcus aureus (MSSA) no. (%)	8	1 (9%)	7 (28%)
Methicillin Resistant Staphylococcus aureus (MRSA) no. (%)	4	2 (18%)	2 (8%)
Coagulase-Negative Staphylococcus aureus (CoNS) no. (%)	2	0 (0%)	2 (8%)
Klebsiella pneumoniae (K. pneumoniae)	4	1 (9%)	3 (12%)
Escherichia coli (E.coli)	4	2 (18%)	2 (8%)
Enterobacter cloacea	1	0 (0%)	1 (4%)
Morganella morganii	2	1 (9%)	1 (4%)
Pseudomonas aeruginosa	6	1 (9%)	5 (20%)
Mycobacterium tuberculosis (M. Tb)	2	0 (0%)	2 (8%)
Staphylococcus epidermidis	1	1 (9%)	0 (0%)
Acinetobacter baumannii	1	1 (9%)	0 (0%)
Staphylococcus hominis	1	1 (9%)	0 (0%)

## Discussion

This study found a comparable risk of post spinal surgery SSIs between topical vancomycin users and non-users. Nevertheless, the findings of the original and sensitivity analyses showed that the usefulness of topical vancomycin in this context would benefit from the conduct of additional multicenter studies with the inclusion of a larger number of patients.

The risk of post-spinal surgery SSIs between topical vancomycin user vs. the non-user groups in our study was found to be comparable, which was similar to the findings of two-third of the published studies (20 of 30 [67%]) that assessed the effectiveness of vancomycin in this patient group [13–41]. The risk in the topical vancomycin group in the largest of those studies varies from being lower, to comparable, or even higher vs. the non-user groups. Nevertheless, the analysis of this risk in most of the published studies was not adjusted for the known measured confounders, and the risk of confounding by indication was taken into account only in two of these studies [25, 27, 28, 32, 33, 38]. Additionally, the risk in two of the largest studies was assessed without a control group (i.e. in a pre and post fashion) [25, 27]. The evidence from three randomized controlled trials was not conclusive since two trials were open-label, and two of were stopped prematurely [17, 37, 41]. The risk of SSIs in our study was comparable to that in the two studies in which confounding by indication was taken into account by propensity score analysis [28, 38]. The propensity score model in our study showed that the use of topical vancomycin is being channeled to the group of patients who are at higher risk of post-spinal surgery SSIs. Doses of topical vancomycin in the published studies ranged from 0.5 to 2 g, most utilized a prophylactic cefazolin dose, and most were designed as retrospective cohort studies. The findings of our study showed that the distribution of Gram positive and polymicrobial/Gram negative SSIs was similar in both groups. This was different from their distribution in most published studies in which the risks of Gram positive pathogens (i.e. Staphylococcus species) and polymicrobial/Gram negative pathogens in the vancomycin-treated group were lower and higher, respectively [42, 43].

Our study was the first to assess the effectiveness of topical vancomycin in minimizing the risk of post-spinal surgery SSIs in the Gulf region. Additionally, it was one of the few observational studies in this context that took confounding by indication into account with a good level of completeness of the measured confounders. Another strength in the study was the sufficient follow up period (30–90 days) giving that 30-days follow up by the same surgeon was completed for almost 94% of the patient population rendering the risk of outcome misclassification. The main limitation in our study was that it was limited to a single center. The inclusion of more centers (especially the largest ones) in future studies would improve the generalizability of the assessment.

## Conclusions

To conclude, we could not find a lower risk of post-spinal surgery SSIs with the use of topical vancomycin. Further studies are needed to assess benefits of using topical vancomycin for this indication vs. the risk of antimicrobial resistance.

## Abbreviations

SSIs

surgical site infections, MRSA:methicillin-resistant staphylococcus aureus, OR:odds ratio, IPTW:inverse probability of treatment weighting, ICD-10:International Statistical Classification of Diseases and Related Health Problems 10th Revision, BMI:body mass index, SMD:absolute standardized difference.

## Declarations

**Ethics approval:** A protocol for the study was submitted to the Institutional Review Board (IRB) at the hospital and an approval was granted on 5/2019 by the IRB.

### Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [patient confidential data] but the anonymized datasets are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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## Figures

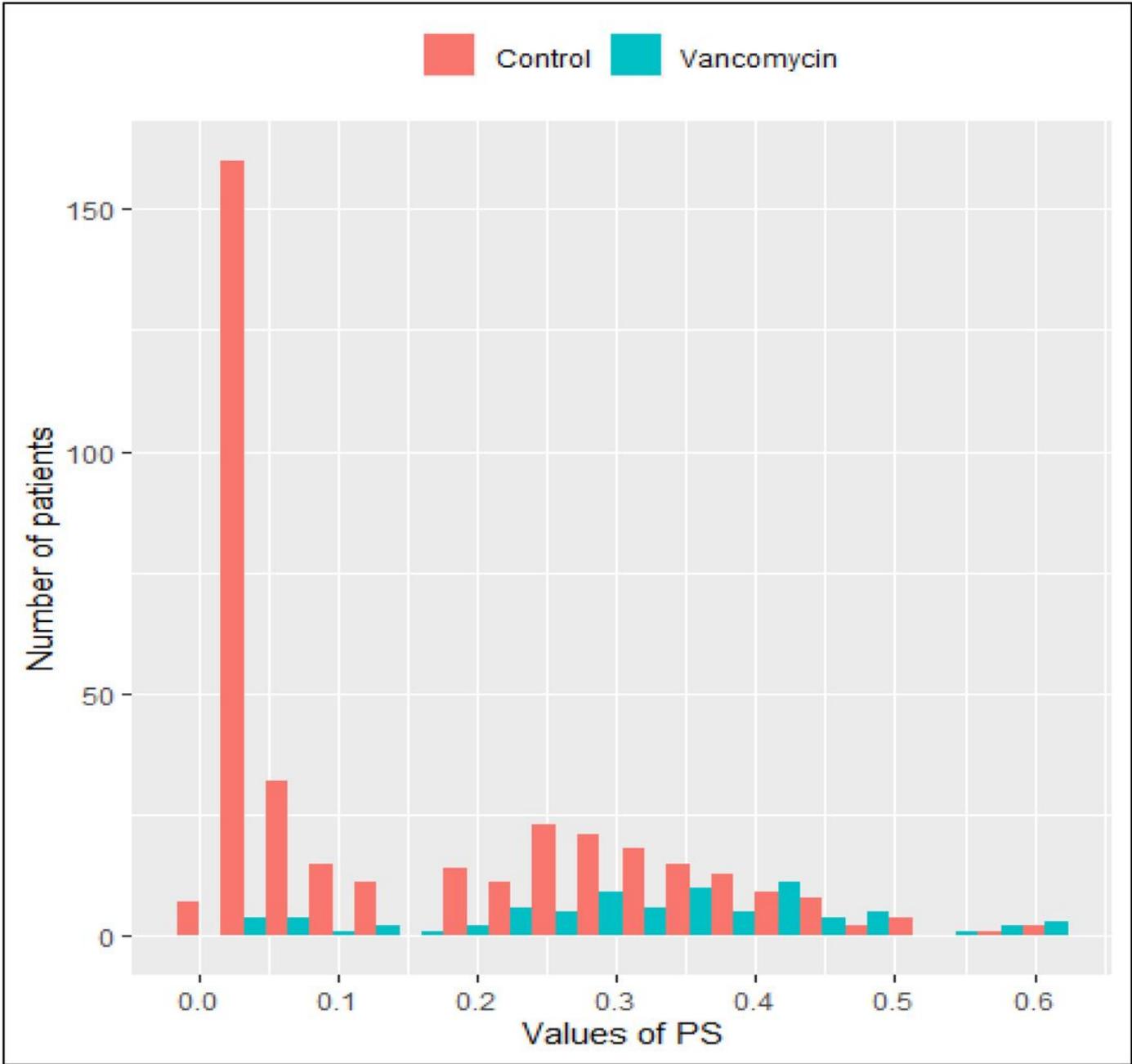


Figure 1

Propensity score distribution in the vancomycin (test) vs. control (non-user) groups