Infectious Prophylaxis with Intrawound Vancomycin Powder in Orthopedic Surgeries: Systematic Review with Meta-Analysis*

Profilaxia infecciosa com aplicação local de vancomicina em pó em cirurgias ortopédicas: revisão sistemática com metanálise

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Abstract

Despite many existing strategies used to reduce the rates of surgical site infection (SSI), these are still fairly frequent complications that pose a challenge for orthopedic surgeons. Therefore, the search for more effective methods of perioperative infection prophylaxis became a main subject of research, with the goal of decreasing postoperative morbidity, mortality, and costs. Thus, the present study sought to assess the effectiveness of intrawound vancomycin powder in orthopedic surgery SSI prophylaxis.

A systematic review and meta-analysis study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2015 (PRISMA-P 2015). A comprehensive literature search was performed to identify controlled studies on the rates of SSI with or without the local use of vancomycin powder. Exclusion and inclusion criteria were applied. A meta-analysis with random effects was performed.

Out of 412 titles that met the criteria, 7 studies regarding spine surgery were included: 4 prospective and 3 retrospective studies. A total of 6,944 cases were identified, and they were divided into 2 groups: the control group (3,814 patients), to whom intrawound vancomycin was not administered, and the intervention group (3,130 patients), to who vancomycin was administered locally. We observed that 64 (2.04%) patients in the intervention group developed SSI, in contrast to 144 (3.75%) patients in the control group. The results of the meta-analysis showed that the local use of vancomycin powder had an statistically significant protective effect against SSI in cases of spine surgery, with a relative risk (RR) of 0.59 and a 95% confidence interval (95%CI) of 0.35–0.98.

Keywords

- vancomycin
- surgical wound infection
- orthopedics

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The use of prophylactic intrawound vancomycin powder has a protective effect against SSI in spine surgeries; however, further prospective trials are needed to endorse its use in orthopedic surgeries.

Resumo

Apesar das diversas estratégias perioperatórias empregadas para diminuir a incidência de infecção no sítio cirúrgico (ISS), tais complicações ainda são frequentes, e representam um desafio para os ortopedistas. Por esse motivo, há uma necessidade permanente de buscar métodos cada vez mais eficazes de profilaxia anti-infecciosa, para que sejam reduzidas significativamente as taxas de morbidade pós-operatória, mortalidade, e os custos com os cuidados de saúde. Este estudo teve como objetivo avaliar a eficácia da profilaxia infecciosa com aplicação tópica de vancomicina em pó em cirurgias ortopédicas.

Fez-se um estudo de revisão sistemática com metanálise, usando-se o Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2015 (PRISMA-P 2015). Fez-se uma busca abrangente na literatura por estudos controlados sobre as taxas de ISS com e sem o uso de vancomicina em pó na ferida.

Entre os 412 títulos encontrados que preencheram os critérios, foram selecionados 7 estudos, 4 prospectivos e 3 retrospectivos, todos em cirurgia de coluna. A amostra total foi de 6.944 pacientes, que foram divididos em 2 grupos: controle (3.814 pacientes) e intervenção (3.130 pacientes). Observou-se que no grupo intervenção, no qual a vancomicina tópica foi aplicada, 64 (2,04%) pacientes desenvolveram ISS, e, no grupo controle 144 (3,75%) pacientes. Os resultados da metanálise demonstraram que o uso de vancomicina tem efeito protetor contra ISS em cirurgias de coluna, com risco relativo (RR) de 0,59, significância estatística, e intervalo de confiança de 95% (IC95%) entre 0,35–0,98.

O uso da vancomicina em pó profilática, no leito da ferida, tem fator protetor contra ISS em cirurgias de coluna; entretanto, mais ensaios prospectivos randomizados são necessários para recomendar seu uso em cirurgias ortopédicas.

Palavras-chave

- vancomicina
- infecção da ferida cirúrgica
- ortopedia

Introduction

Surgical site infections (SSIs) may result in increased postoperative morbidity, mortality, and health care costs. *Staphylococcus aureus* is the major germ causing SSIs. It is estimated that between 15 and 25% of the healthy population are chronic carriers of *S. aureus* and, therefore, present a higher risk of developing SSIs,[1] which are a devastating and costly complication for which prevention has become a relevant objective and recurrent target of research.[2] Its incidence can range from 0.7 to 11.9%, depending on the type of infection, the indication of surgery and the use of instrumentation.

Several perioperative strategies are currently employed to reduce the incidence of infection, some of which are supported by the literature, while others remain under study. These strategies aim at a better response of the host and a decrease in the possibilities of bacterial contamination in the pre-, intra- and postoperative periods.[3] In addition to the usual intravenous prophylactic antibiotics, the administration of topical antibiotics has been advocated as an adjunctive measure to reduce contamination.[4]

Increased resistance to common antibiotics has led to ineffective prophylaxis against more than 50% of all organisms that cause most cases of SSI. Due to this concern, several studies have supported the possibility of introducing vancomycin powder directly into the surgical wound during closure as a prophylactic perioperative procedure.[5] Prophylactic vancomycin powder is highly available, easy to adminidter, and has a low cost. However, there is still a shortage of studies evaluating the efficacy of local intraoperative vancomycin powder and the possible adverse effects and complications that may result from it.[6] It has been observed that the intrawound application of the drug is likely to substantially decrease the rapid absorption in the systemic circulation, thus reducing possible side effects.[7]

Vancomycin is a glycopeptide antibiotic, and its mechanism of action is bactericidal; it acts to inhibit cell wall biosynthesis in Gram-positive bacteria. It is known to have no active effect against most Gram-negative bacteria, due to the particularly different composition of their outer membranes.[8] The critics of this preventive method argue about the possibility of the development of resistant organisms.[9] Despite all of the limitations of the studies on the

effectiveness of vancomycin, until recently the literature has reported results that are mostly positive, and some series have even demonstrated complete success in prophylaxis against SSI.[7]

As for the dose used directly in the wound, the studies have values ranging from 1 g to 2 g, and a recent meta-analysis has suggested that vancomycin may be more effective in preventing infection among high-risk patients.[2] Vancomycin powder, associated with standard systemic prophylaxis in orthopedic surgeries, has been shown to reduce infection rates from 2.6 to 0.2%.[7,10] Therefore, it is essential to use new techniques that can guarantee adequate prophylaxis to the surgical site, and the option of placing topical antibiotics is advantageous, since high concentrations are reached directly in the places of interest (surgical sites), in concomitance with the considerable reduction in systemic toxicity.[11]

The objective of the present study was to evaluate the efficacy of SSI prophylaxis with the use of topical vancomycin powder directly on the surgical wound in orthopedic surgeries.

Methods

This systematic review with meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2015 (PRISMA-P 2015).[12]

An extensive literature search was conducted to identify studies evaluating the efficacy of topical vancomycin powder prophylaxis to reduce the risk for SSI in orthopedic surgeries, and comparing groups that were submitted to the procedure with groups that were not.

The inclusion criteria for the selection of studies were: 1) cohort, clinical trial or case-control studies; 2) studies with a clear description of adult patients (> 18 years of age) to whom vancomycin was administered directly into the operative wound in orthopedic surgeries; 3) studies with control groups to which topical vancomycin powder was not administered; 4) studies written in Portuguese, English and Spanish; and 5) studies included in the databases until 2017.

These criteria were chosen in compliance with the objective of the present study. The languages selected, Portuguese, English and Spanish, are respectively the mother tongue and the languages most used in scientific publications.

We excluded studies with inadequate descriptions and when the clinical outcome was not the one proposed by the authors. Case reports, editorials, case series studies, narrative reviews or systematic reviews and meta-analysis were not considered. Articles that were incomplete or did not provide data about the use of topical prophylactic vancomycin were also excluded. We also did not select articles that presented scores lower than 7 when evaluated by the Newcastle-Ottawa Quality Assessment Scale (NOS),[13] which determines the quality of the study, or that did not fit the necessary classification provided by the Level of Scientific Evidence by Type of Study (of the Oxford Centre for Evidence-Based Medicine) to determine the publication value of the study.[14]

The inclusion criteria are described in ►**Table 1**, and they follow the Patient, Intervention, Comparison, Outcome (PICO) protocol with the purpose of conferring internal validity to the work.

The databases used for the survey were: Medline, SciELO, Cochrane, PubMed and Google Scholar, and the search was performed by three researchers. Doubts and deadlocks were solved with the advice of a more experienced senior researcher, as well as the final selection. The search was performed with the following descriptors: *vancomycin powder*, *intrawound vancomycin*, *orthopedic surgery and surgery prophylaxis*, in English, and *vancomicina em pó*, *vancomicina tópica* and *cirurgias ortopédicas and profilaxia cirúrgica* in Portuguese. Out of the 412 records identified, 7 studies that met the criteria were selected.

The results were presented through an organization chart to select articles according to the PRISMA-P 2015 statement. The dispersion data were presented and compiled as funnel and forest plots for the comprehension of the meta-analysis. The statistical analysis was performed using the Mantel-Haenszel method with random effects, and the relative risk (RR) test with a 95% confidence interval (95%CI). The results of different studies were assembled in a random effect model, since not all of them followed the same methodology. The heterogeneity was analyzed by the Chi-squared (χ^2) test, least squares (L2-norm), and Tau-squared (τ^2) in order to identify differences that could cause biases in the study. These analyses were performed using the Review Manager (RevMan5, The Nordic Cochrane Centre, Copenhagen, Denmark) software, version 5.3, for MacOSX.

Results

►**Figure 1** shows the articles selected. During the search, 412 references were identified as potentially relevant. After the analysis of the title, abstract and language of publication, 339 studies were excluded because they were duplicate studies or works that were not directly related to the objective of the present study, and 73 references remained. Out of these, 66 were discarded based on the quantitative and qualitative

Table 1 Inclusion criteria according to the PICO protocol

	PICO inclusion criteria
Indicators	Results according to the PICO protocol
Project	Cohort studies and case-control clinical trials
Population	Patients undergoing orthopedic surgery with and without the prophylactic administration of vancomycin powder directly at the surgical site
Intervention	Prophylaxis: vancomycin topical powder
Comparison	No prophylactic topical administration of vancomycin powder
Outcome	Rates of incidence of surgical site infections

Abbreviation: PICO, Patient, Intervention, Comparison, Outcome.

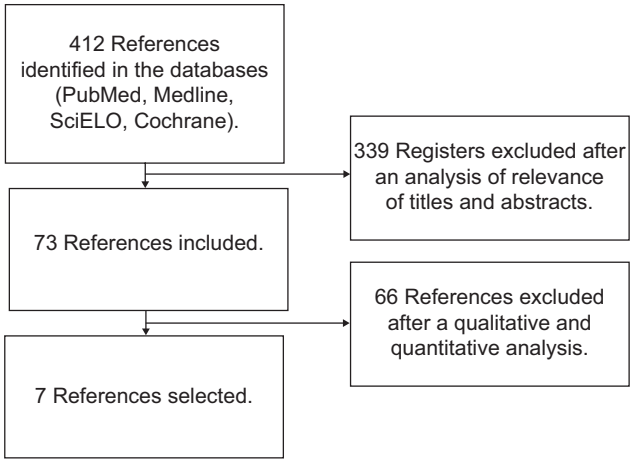

Fig. 1 Organizational chart for the selection of articles - PRISMA-P 2015.

analysis of the records. In the end, 7 articles remained in the present study as eligible for meta-analysis.

We used as exclusion criteria: 1) works without a control group; 2) studies among the pediatric population (< 18 years of age); 3) studies with a population with comorbidities (due to the risk of bias not attributable to the general population) and with patients with established infections; 4) cost-analysis studies; 5) pharmacological studies; 6) pilot studies; 7) presentations in annals and congresses; 8) studies with historical control; 9) case reports; 10) studies in vitro and with animal models; and 11) editorials, comments and letters. We opted for the exclusion of works with historical controls, even those that described all of the cases of a single surgeon, due to the risks of biases inherent to the technological evolutions and surgical technique, which invariably occur over time and are difficult to control by the authors of the studies.

We have only included controlled studies evaluating the use of topical powder vancomycin for perioperative prophylaxis in orthopedic surgeries. Out of these seven, four are prospective studies (two clinical trials) and three are retrospective cohort studies, and all are comparative studies in the field of spinal surgeries. In them, the control groups are those in which the patients were only submitted to the standard venous antibiotic prophylaxis, and the intervention groups are composed of those who were submitted to vancomycin powder in the wound bed. Both groups in the seven studies underwent the same pre-surgical preparation, as well as identical venous antibiotic prophylaxis, according to the standardization of each service, in order to better homogenize the samples.

Of the seven articles included, five were in favor and two were against the use of powdered vancomycin as a prophylactic measure against SSIs in spine surgeries, the latter being randomized trials, but without blinding. ►**Tables 2** and **3** summarize the main aspects of the works included in the present study.

►**Figure 2** summarizes in a forest plot the meta-analysis of the selected studies, considering the SSI as the outcome. The total sample was composed of 6,944 patients, who were divided into 2 groups: control (3,814 patients) and intervention (3,130 patients). ►**Figure 2** also shows that in the intervention group, 64 (2.04%) patients developed SSIs, as opposed to 144 (3.78%) patients in the control group. The use of topical vancomycin had a protective effect against SSIs, with an RR of 0.59, with statistical significance (95%CI: 0.35-0.98). It is possible to observe heterogeneity of 52% with L2 associated with a *p*-value of 0.05 of the χ^2 test. Thus, conclusions based on this analysis may have their value compromised due to the high heterogeneity among the studies.

►**Figure 3** shows the summary in a funnel plot of the meta-analysis of the selected studies considering the publication bias – the X axis is in logarithmic function. It is possible to observe that the studies present in visual analysis the distribution of symmetry with the presence of only one outlier. The analysis with only seven studies does not enable us to draw conclusions about the presence of publication biases.

►**Figure 4** summarizes in a funnel plot the meta-analysis of the selected studies considering as a result the presence of SSI. The use of vancomycin had a protective effect on deep SSIs, but without statistical significance due to the broad spectrum of the 95%CI (0.44–1.06).

It is possible to observe heterogeneity of 68% with L2 associated with a *p*-value of 0.004 of the χ^2 test. Thus, conclusions based on this analysis may have their value compromised due to the high heterogeneity between the studies.

Discussion

SSIs represent an significant surgical complication,[15] leading to an increase in postoperative morbidity and mortality and a considerable increase in health costs, with a frequent need of multiple surgical debridements, prolonged hospitalization and long-term antibiotic therapy.[1] Several perioperative strategies are currently employed to reduce the incidence of infection[3] and the increased bacterial resistance to cephalosporins, which are widely used as intravenous surgical prophylaxis, especially considering methicillin-resistant *Staphylococcus aureus* (MRSA);[16] this has led to the search for new options of SSI prophylaxis over the years. The intravenous use of vancomycin has not been shown to be superior, and there is an association with complications such as renal insufficiency and bacterial resistance, as well as low penetration in the spinal region.[17] Antibiotics applied at the operative site have been widely used over the years for the treatment and prevention of infections and osteomyelitis, mainly mixed in bone cement.[11,18,19] Several studies have been developed to investigate absorbable vehicles for local antibiotics in order to avoid the need for surgical removal of infected wounds.[20,21] Applying antibiotic powder directly on the wound would be a viable, safe and cost-effective strategy,[22] with several recent publications reporting the possibility of applying vancomycin powder directly onto the surgical wound bed, prior to its closure, as an effective perioperative prophylactic measure, especially in spinal surgeries.[23]

Table 2 Summary of the seven articles included

							Infection			
Authors and year of publication	**Study design**	**Level of evidence**	**Follow-up**	**Sample**	**Intervention group**	**Control group**	**Vancomycin**	**Control**	**Type of spinal surgery**	**Difference between groups**
O'Neill et al,[20] 2011	Retrospective case review	3	C: 30 weeks; V: 24 weeks (mean) > 2 m:C - 73%; V - 80%	110	56	54	0%CI : 06% $p = 0.02$	7 (13%) 5 - 25%CI 5 deep 2 superficial	Posterior fusion; instrumentation (traumatic lesions)	Similar Characteristics between the groups ($p > 0.05$)
Tubaki et al,[11] 2013	Controlled randomized prospective essay	2	Min. 12 weeks	907	433	474	7 (1.61%) 6 deep 1 superficial 6 instrumented	8 (1.68%) 6 deep 2 superficial 6 instrumented	Open; instrumented or not; any level	Similar distribution between the groups (randomized)
Hill et al,[25] 2014	Comparative retrospective cohort	3	Min. 1 month; C - 10.03 months V - 8.76months	300	150	150	3% superficial (10/300) 5/150 Deep 0% (95%CI: 0–2.4%) ($p = 0.0297$)	5/150 4% (n = 6) (95%CI: 1.5–8.5%)	Instrumented or not posterior access	$p < 0.05$: age, lumbar surgery, MD, type of surgery, surgery duration (covariate analysis with no difference for predictors of deep SSI)
Devin et al,[28] 2018	Prospective multicentric observational (secondary analysis)	2	30 days	2,056	966	1,090	Total SSI: 2.2% (n = 21)	5.1% (n = 56)	Elective (degenerative, tumoral, trauma)	$p < 0.05$: Intervention group: more MD, corticoid use, arthrodesis
							$p < 0.001$ RR: 2.5 (95%CI: / 1.5–4.1)			
							Deep SSI: 0.7% (n = 7)	3.9% (n = 42)		
							$p < 0.001$ RR: 5.9 (95%CI: 2.6–13.2)			
Hey et al,[6] 2017	Comparative retrospective cohort	3	30-90 days	389	117	272	18/389 (4.6%) 1 (0.9%) 1 deep	17 (6.3%) 10 deep 7 superficial	Open, instrumented	$p < 0.05$: smoking, spine pathology, surgical access, blood loss, OR surgery duration adjusted for SSI: smoking and duration; $p > 0.05$
							$p = 0{,}0495$ / OR: 0.13 (95%CI: 0.02–0.99)			
Chotai et al,[27] 2017	Observational prospective 2 cohort	2	90 days	2,802	1,215	1,587	1.6% (n = 20)	2.5% (n = 40)	Elective; with or without instrumentation, degenerative or oncological	Similar characteristics between the groups ($p > 0.05$)
							All deep (return to SC); $p = 0.02$			
Mirzashahi B et al,[26] 2018	Controlled randomized prospective essay	2	90 days	380	193	187	Total: 3.9% 5.2% (n = 10) All deep $p = 0.2$	2.7% (n = 5)	Open (tumoral, degenerative, trauma, deformities); posterior access	Similar distribution between the groups (randomized)

Abbreviations: 95%CI, 95% confidence interval; C, control group; m, Month; MD, diabetes mellitus; OR, odds ratio; RR, relative risk; SC, surgical center; SSI, surgical site infection; V, vancomycin group.

Table 3 Summary of the seven articles included

Authors and year of publication	Dose/Vancomycin application	Infection Criteria	Microbiological profile[b]	Vancomycin Complications	Antibiotic Prophylaxis IV (anesthesic induction + duration)	Number of Instituitions/ surgeons	SSI treatment	Conclusions
O'Neill et al,[20] 2011	1 the g over fascia, muscle and SCCT, avoiding the dura and the bone graft	Superficial - wound inspection Deep - axial imaging s/n (MRI)	Deep SSIs (5): MRSA 4/5; Polyflora: 1/5. Superficial SSIs: no culture (no debr.)	None	Cefazolin 1g + 1g 8/8 h 24h Allergy: clindamycin 900 mg	Unicentric Intervention - 01; control: multiple	2 superficial: local care and ATB 5 deep: debr. + ATB IV 01 death	The topical use of powdered vancomycin has protective effects against SSIs
Tubaki et al,[11] 2013	1 g over the fascia, muscle and SCCT, avoiding the dura and the bone graft	Superficial and deep. Diagnostic method not specified.	C: 1 *E. coli* and 2 *S. aureus*. V: 1 *S. aureus* and 2 *Klebsiella*	None	Cefuroxim 750 mg + 750 mg 8/8 24-48h	Unicentric: multiple	Superficial: local care + ATB; deep: debr. + ATB IV	Vancomycin powder has no protective effect against SSIs and may not be effective when the basal rate of infection is low.
Hill et al,[25] 2014	1-2 g directly over the whole exposed tissue	Superficial - skin; deep - TCSC subfascial	Gram + in 4/6 deep SSIs (66.7%): 4 MRSA; 1 *Enterococcus* (control group)	None	Cefazolin 1g + 2g 8/8 h 24h Allergy: Vancomycin	Unicentric: Intervention - 01; Control - 01	Superficial: wound care or cephalexin OA 10 days; deep: irrigation; surgical debr. + ATB OA or IV; 6 SSIs (control): 12 debr.	Topical vancomycin may be effective, especially in deep SSI prophylaxis that requires surgical debridement
Devin et al,[28] 2018	1 g/10 cm of incision over the fascia, muscle and SCCT, avoiding the dura and the bone graft	Visual aspect of operatory wound + MRI with contrast for all cases of suspicion. Deep: return to SC	Does not apply	None	Cefazolin 1g + 1g 8/8 h 24h Allergy: clindamycin 900 mg	Multicentric: multiple	Superficial: empirical ATB OA Deep: debr. +/- Implant removal +culture with ATB IV + av. infectologist	Topical vancomycin reduces the risk of SSI and the prospect of returning to the SC.
Hey et al.,[6] 2017	1 g directly over the whole exposed tissue	Independent and trained nurse. CDC definition for deep or superficial SSIs[a]	General: *P. aeruginosa* - 6 (35,2%); MRSA - 4 (22%). V: 1 *P. aeruginosa*; C: 4 MRSA; 1 coagulase-negative staphylococci; 1 *Bacillus cereus*; 5 *P. aeruginosa*; 2 *E. coli*; 3 *Klebsiella pneumoniae* ($p < 000.1$ for causing microorganism)	None	Cefazolin 1g + 1g 8/8 h 24h Allergy: vancomycin 1 g	Unicentric: Multiple (intervention- 03; control-03)	13 out of 18 with SSI; surgical treatment: 01 V -fusion revision + debr. +ATB 3 months; 10 C - debr.; 2 C - debr. + implant removal	Topical vancomycin significantly reduces the morbidity and the rate (shorter time of onset and duration) of SSIs in instrumented surgeries, with *P. aeruginosa* being the main germ.
Chotai et al,[27] 2017	1 g/10 cm of incision over the fascia, muscle and SCCT, avoiding the dura and the bone graft	Visual aspect of operatory wound + MRI with contrast for all cases of suspicion. Deep = return to SC	V: less *S. aureus* (32%/65%; $p = 0.003$); More gram-; Ø vancomycin-resistant *S. aureus*. 1° *S. aureus*: 57%, 2° *S. epidermidis*: 5%	None	Cefazolin 1 g + 1 g 8/8h 24h Allergy: clindamycin 900 mg	Unicentric: multiple	Superficial: empirical ATB OA; deep: debr. +/- implant removal + culture with ATB IV + av. infectologist	Topical vancomycin significantly reduces the risk of SSI and is not related to the increase in MRSA

Table 3 (*Continued*)

Authors and year of publication	Dose/Vancomycin application	Infection Criteria	Microbiological profile[b]	Vancomycin Complications	Antibiotic Prophylaxis IV (anesthesic induction + duration)	Number of Instituitions/ surgeons	SSI treatment	Conclusions
Mirzashahi et al,[26] 2018	1 g or 2 g (2 g for obese patients or > 3 fusion levels) directly over the wound	Definition of the CDC for deep or superficial SSIs	V: *Acinetobacter* and *P. aeruginosa* (20%); C: *S. aureus* and *Acinetobacter*; (40%) 1 MRSA	None	Cefazolin 1 g or 2 g Allergy: clindamycin 900 mg	Unicentric: multiple	Deep (all): debr. + irrigation + ATB IV and av. infectologist No implant removal	Topical vancomycin Is not related to the reduction in the risk of SSI, but may change SSI microbiological profile

Abbreviations: ATB, antibiotic; av, avaliation; C, control group; CDC, Centers for Disease Control and Prevention; debr., surgical debridement; E. coli, *Escherichia coli*; Gram-, Gram-negative bacteria; Gram +, Gram-positive bacteria; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MRI, magnetic ressonance image; P. aeruginosa, *Pseudomonas aeruginosa*; S. aureus, *Staphylococcus aureus*; w/n; SC, surgical center; SCCT, subcutaneous tissue; SSI, surgical site infection; V, vancomycin group; OA, oral administration.

Notes: [a] Criteria for the definition of SSI according to the CDC: culture +; clinical signs of hardening, edema, heat, hyperemia and festering incision Superficial: 30 days; skin and SCCT. Deep: 90 days; fascial and muscular layers.

[b]Results of cultures made in cases submitted to surgical debridement (deep SSIs).

Pharmacokinetic studies have considered the topical use of vancomycin powder over the operative wound bed as a safe measure. This modality of use reaches high therapeutic and concentration levels of the antibiotic in the operative wound and excellent minimum inhibitory concentration (MIC), for resulting low toxic and serum levels.[24]

In the present meta-analysis, we found that the topical use of vancomycin powder has a protective effect against SSIs in spinal surgeries (RR: 0.59), with statistical significance (95%CI: 0.35–0.98). However, the heterogeneity among the studies cannot be neglected (L2 = 52%, $p = 0.05$), as well as the different study designs, which cause confusion in the results. Generally, the samples are not randomized, homogenous or controlled regarding the indications of surgeries (trauma, degenerative disease, tumor, deformities etc.), the instrumentation or lack thereof ,the known risk factors for SSI (diabetes, obesity and smoking, for example), the follow-up time, the method and dose of topical vancomycin, or the SSI diagnostic criteria, be it a deep or superficial SSI. In the analysis of the deep SSI alone, we observed a protective effect of vancomycin, but without statistical significance, probably due to the high heterogeneity (L2 = 68%; $p = 0.004$). The greater clinical and economic impact of deep SSIs, which increase morbidity, mortality, and costs, requiring surgical reapproaches, longer hospitalization time, long cycles of venous antibiotics and delayed rehabilitations, tends to draw more attention from the authors of the studies than the analysis and prevention of this more morbid type of infection, although superficial infections should not be overlooked, as they also demand prompt diagnosis and rapid therapeutic intervention.

Of the seven papers included in the present review, five found a protective effect with the use of powdered vancomycin as a statistically significant measure for SSI prevention – three retrospective cohort studies[20,25,26] and two prospective studies, all with level of evidence[27,28] Two demonstrated no benefit from the use of vancomycin,[11,26] and both are randomized and controlled prospective trials. All of the studies included dealt with the method in question for the prevention of SSIs in spinal surgery. A few studies were found regarding other types of orthopedic surgeries, but they were not included in the present analysis because they did not fit the selection criteria (studies with a historical control group for example).

All retrospective cohort studies included[20,25,29] found statistically significant values of reduction in SSI rates in spinal surgery with the adminidtration of vancomycin powder to the surgical wound before its closure. There was, however, no standardization in the time of postoperative follow-up, dose and method of application, or standardization of the SSI criteria. However, a statistically significant reduction was observed in deep SSIs in relation to superficial SSIs; one of the studies[29] presented the same proportion of cases (5 in 150 individuals in each group): these data were not considered for the statistical analysis of significance, because they could produce a bias. However, there was no need to return to a surgical center for debridement in any patient in the intervention group, whereas in the control group, 6 patients required a new intervention, totaling 12 new procedures. However, it is not possible to neglect the

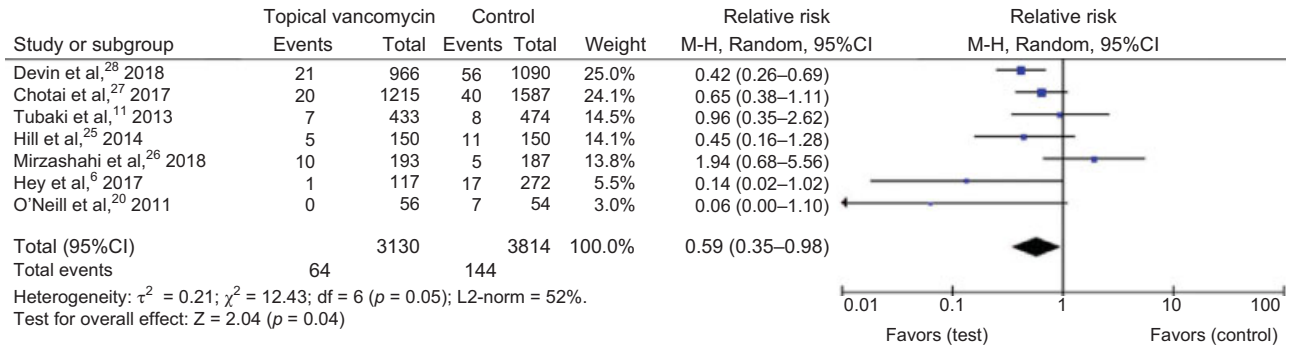

Fig. 2 Forest plot comparing the topical administration of vancomycin with the control group in the prevention of surgical site infections.

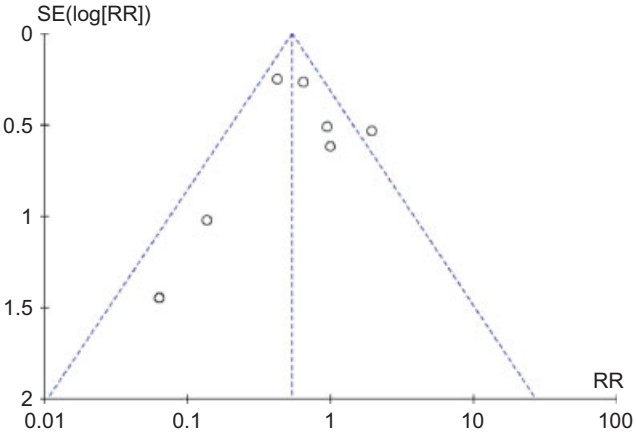

Fig. 3 Funnel plot comparing publication bias among the studies included in the present review.

remarkable reduction in the rates of infection in the intervention group in the other studies. The follow-up time also varied, and a minimum of 30 days or 4 weeks was observed in all three studies,[20,25,29] a period of time that may be considered short to assess complications, but enough for the emergence of most SSIs.[30]

There were also limitations regarding the samples studied in these works. Hill et al[25] recognized that the groups presented differences concerning the distribution of known risk factors – a significantly younger intervention group, a lower prevalence of diabetes and a lower number of lumbar procedures –, but the covariate analysis did not associate this with a higher risk of infection. In the work by Dennis et al,[29] a significant difference was observed in the distribution of the following characteristics: smoking (greater in the control group); preoperative diagnosis (plus degenerative disease in the control group and more developmental disease in the intervention group); surgical access (posterior route predominant in the intervention group); blood loss and surgical time (higher in the intervention group). The intervention group had higher rates of posterior access, blood loss and surgical time, which are factors expected to increase the risk of infection. However, in a multivariate analysis, the opposite was observed. The hypothesis that the topical use of vancomycin powder reduces the risk of SSI was reinforced. O'Neill et al[20] considered as limitations of their sample that not all risk factors contributing to the emergence of infection were susceptible to evaluation and control (such as the nutritional status); since the time of surgery was statistically longer in the control group ($p = 0.01$), it is not possible to know for sure how much this factor contributed to the increase in infection rates; the sample did not have a sufficient number of patients for the study to reach a power of 80%: the calculated power of the study was of 66%.

Among the prospective studies, two,[27,28] with a level of evidence 2, favored the use of vancomycin powder for the prevention of SSI in spinal surgery, with a statistically significant protective effect, both for the occurrence of SSI and SSI with a need to return to the surgical center (the deep type). Both used the same criteria to define superficial or deep infections, the same standardization of the topical vancomycin dose (1 g/10 cm incision) and the same venous antibiotic prophylaxis. The authors treated with new surgeries for debridement only the deep infections.

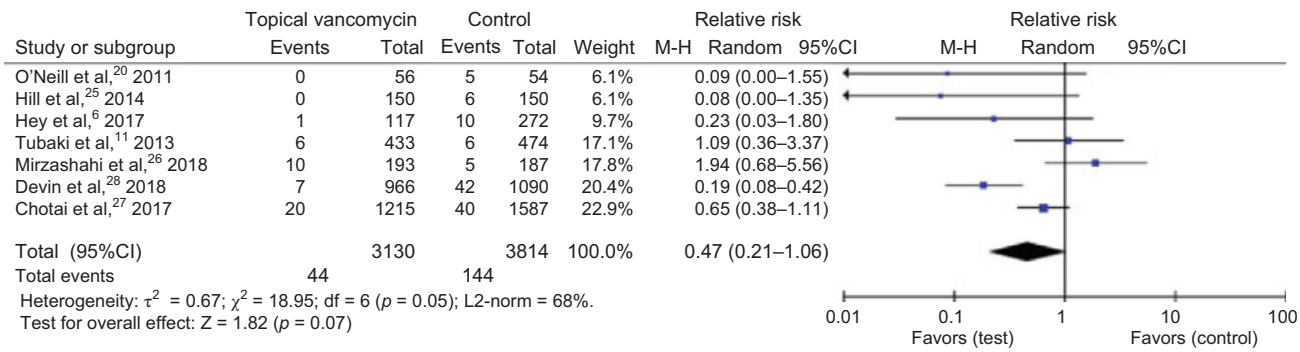

Fig. 4 Forest plot comparing deep surgical site infections treated with topical vancomycin versus the control group.

However, the two prospective randomized clinical trials[20,26] with level of evidence 2 included in the present study did not find a statistically significant difference for the reduction in the rate of SSI with the intrawound application of vancomycin powder. Neither work has used blinding. In the study by Tubaki et al,[11] the calculation of the sample and the definition of the criteria for the classification of superficial or deep SSIs were not reported, and, although no differences between the groups were reported, confounding risk factors that are known to increase the occurrence of SSIs were not evaluated. There were no differences regarding the reduction in infection rates with the topical application of vancomycin; however, the basal infection rates were already remarkably low (1.68%). Mirzashahi et al[26] conducted a unicentric study with standardization of the vancomycin dose of 1 g (2 g in the case of obese patients or more than 3 levels of arthrodesis), and used the definition criteria of SSI recommended by the Centers for Disease Control and Prevention (CDC), observing a follow-up time of 90 days. They concluded that there is no evidence to recommend the use of topical vancomycin for the prevention of SSIs in spinal surgeries, but they emphasized the change in the microbiological profile of SSI as a serious repercussion to be evaluated in future studies: in their intervention group, *Acinetobacter* and *Pseudomoas aeruginosa* were the predominant microorganisms, and, in the control group, *S. aureus* and *Acinetobacter* prevailed (►**Table 2**).

None of the studies included in the present review found adverse effects associated with the topical intraoperative application of vancomycin. Only one study (a case report) was found with reports of circulatory collapse after the topical application of vancomycin,[31] and the authors themselves state that it may have been caused by an anaphylactoid reaction to the antibiotic, but it may also have occurred as a consequence of the considerable loss of two liters of blood during the surgical procedure, or as a consequence of an anaphylactic reaction to other drugs administered during anesthesia. Another study, which is also a case report,[32] establishes the use of powdered vancomycin as a possible cause of sterile seroma after an extreme lateral interbody fusion (XLIF) procedure. The authors mention a possible allergic reaction to the antibiotic as a cause, but emphasize the presence of confounding variables and the need for studies with a larger population.

A recurrent concern regarding the use of topical vancomycin as surgical prophylaxis would be the risk of selecting resistant microbial flora or changing the microbiological pattern of the SSI. The studies included in the present review that found infections in the intervention group showed a greater tendency towards a reduction in *S. aureus* infections (including MRSA) and an increase in *P. aeruginosa* infections.[22,26,27,29]

Regarding orthopedic surgeries, particularly the spine specialties, vancomycin powder in the surgical incision has been adminidtered and defended by several authors; it has been the object of several studies, from observational studies to clinical trials with case and control groups, due to its low cost, low potential for toxicity, and ease of administration, without increasing the surgical time and the changes in the operative routine. It is noted, however, that there is no standardization regarding the dose and method of application of intrawound vancomycin powder, although there is a tendency to use 1 g.[11,20,25,29] Mirzashahi et al[26] used as criteria 2 g in the case of obese patients and fusion of more than 3 levels. Devin et al[28] and Chotai et al[27] used as criteria the size of the incision: 1 g of vancomycin for each 10 cm of incision. However, these parameters can be considered empirical.

Although the present review included mostly prospective studies (four, while three are retrospective), all of them had levels 2 or 3 of evidence, which is an inherent limitation of the present study. Another limitation was the small number of works included, due to more rigorous exclusion criteria, which limit the sample, as well as the small amount of clinical trials. The present study aimed to evaluate the efficacy of vancomycin powder prophylaxis in orthopedic surgery in general terms, but the field of study outside spinal surgery is still incipient, with few published works; therefore, it is not possible to make a direct inference of the benefits of the methods for other types of orthopedic surgery.

However, more prospective and randomized studies are required for a more secure and supported recommendation of the topical administration of vancomycin powder for SSI prophylaxis, to ensure sample homogenization and control of risk factors (instrumentation or lack thereof, for example), standardization of the dose and technique for the topical use of the antibiotic, determination of the minimum effective local concentration, evaluation of the risk of selection of resistant flora or of changes in the microbiological profile of SSI, selection of the profile of patients eligible for topical prophylaxis (patients with risk factors and centers with high SSI rates appeared to perform better). The use of blinding would also add value to future studies, with elimination of biases such as preferences of the surgeon and peculiarities of the surgical techniques.

Conclusion

The topical administration of vancomycin powder on the surgical wound bed is effective regarding prophylaxis, and has a statistically significant protective effect against SSIs in spinal surgery. It is not possible, however, due to the low number of randomized and controlled clinical trials that have been performed to date, with homogeneous samples capable of proving its benefit. The recommendation for the routine administration of vancomycin powder as prophylaxis against SSIs is promising. Further studies regarding the various types of orthopedic surgeries are needed to extend this measure beyond the field of spine surgeries.

Conflicts of Interest
The authors have none to declare.

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