Spine surgery - the use of vancomycin powder in surgical site for postoperative infection prevention

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

METHODOLOGY FOR EVIDENCE COLLECTION

This guideline followed the pattern of a systematic review with evidence collection based on the movement of Evidence-Based Medicine, in which clinical experience is integrated with the ability of critical analysis, rationally applying scientific information, thus improving the quality of medical assistance.

We used the structured version of the PICO question, in which **P** refers to **patients who underwent spine surgery**; **I** stands for intervention, in this case the use of topical **vancomycin power during surgery (intraoperative)**; **C** stands for control formed by **patients who underwent spine surgery and did not use this antibiotic**; and **O** meaning outcome, in this case the **infection rates and postoperative complications**.

Through the elaboration of relevant clinical questions related to the proposed theme, based on the structured question, we identified the keywords that served as the basis for searching the databases: Medline - PubMed; Embase - Elsevier; Lilacs - Bireme. A total of 27 studies were selected to answer the clinical questions **(Annex I)**.

CLINICAL QUESTIONS:

What is the effect of the vancomycin powder applied directly on the surgical site on postoperative infection rates for patients who undergo spine surgery?

Are there any complications or adverse effects to patients when the vancomycin powder is used?

What is the recommended dose of vancomycin powder to be inserted in the surgical site to prevent infections in dorsal surgical approaches in the spinal column?

GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE:

A: Experimental or observational studies of higher consistency

B: Experimental or observational studies of lower consistency

C: Case reports (uncontrolled studies)

D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models

OBJECTIVE

The objective of this review is to use primary studies to assess the effect of the use of intraoperative vancomycin power as a prevention for postoperative infections in the spinal column, its adverse reactions or complications, and the recommended dose.

CONFLICT OF INTEREST

There are no conflicts of interest to be declared by any of the participants regarding this review.

INTRODUCTION

Postoperative infections after spine surgeries are relatively frequent complications with great morbidity, such as increased length of hospital stay, need for reapproaches, worse functional prognoses, loss of instrumentation, amongst others[1,2].

The incidence of infections at the surgical site in spine surgeries depends of many factors, varying from 0.5% to 15% with higher rates for instrumented surgeries and deformities[3]. Staphylococcal infections (S. Aureus and S. epidermidis) are the most common agents, with increased incidence of methicillin-resistant S. aureus (MRSA)[4,5].

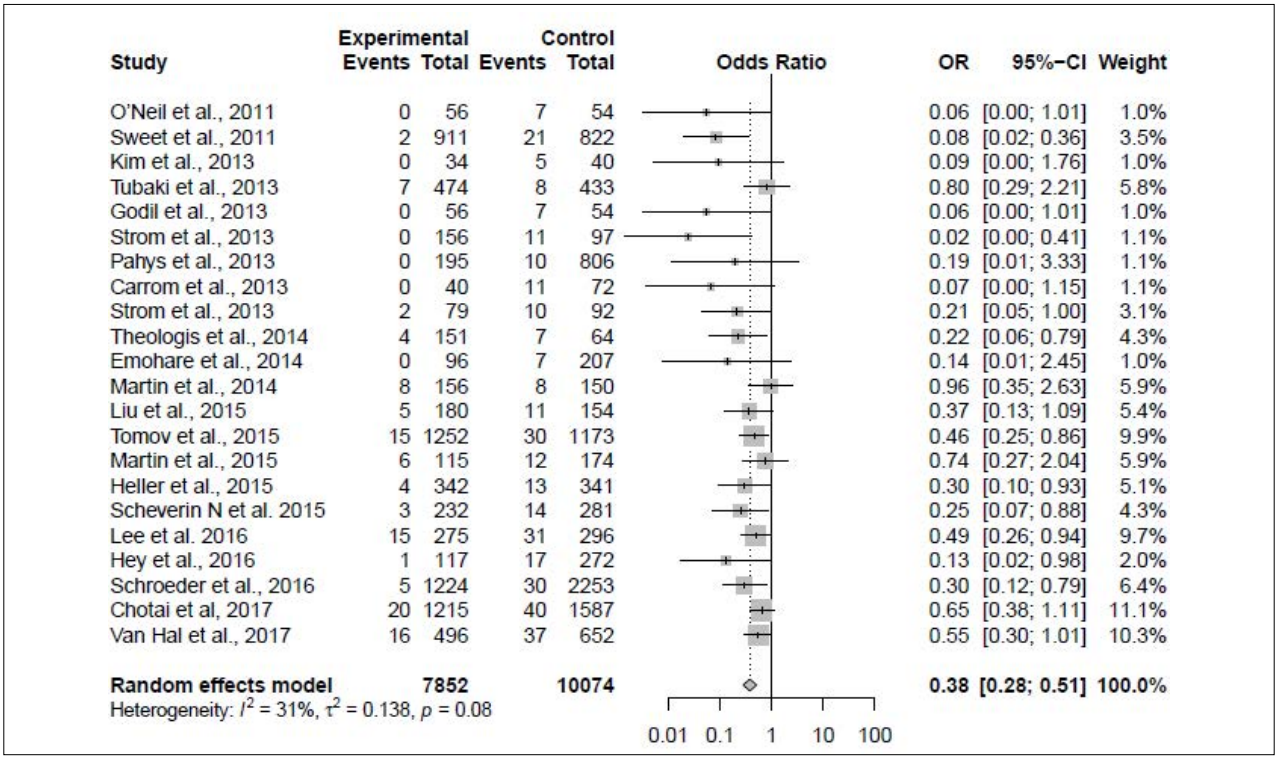
Amongst measures to reduce infection rates, is intravenous antibiotic therapy, with proven but limited effectiveness. Recently, some studies suggested the use of vancomycin powder applied directly to the surgical site can reduce the incidence of infection in spine surgery without relevant additional risks[6]. In this context, it is of the utmost importance to assess the effectiveness of the use of vancomycin powder at the surgical site to prevent infections, as well as the safety of its use.

PRESENTATION OF RESULTS

1. What is the effect of the vancomycin powder applied directly on the surgical site on postoperative infection rates for patients who undergo spine surgery?

The number of combined studies was 22[5-26](B) The only randomized study had an infection rate too low to show the effect. Using the same infection rate of the study and considering a test power of 80%, an estimated error of 5%, and type B error of 5% of 20%, the sample size necessary to reveal the effects would be over double the one used. Thus, the study was demoted regarding methodological quality and evaluated as part of a group along with the other

TABLE 1 - META-ANALYSIS OF THE GROUPED RESULTS



Number of combined studies: k = 22. Odds Ratio: 0.380395%-CI [0.2810 0.5146;] z=-6.26 p-value<0.0001. Random effects model. Quantification of heterogeneity: tau^2 = 0.1380; H = 1.21 [1.00, 1.57]; I^2 = 31.5% [0.0%; 59.2%]. Test for heterogeneity: Q=30.64 d.f.= 21 p= 0.0798

studies. The odds ratio of infection with the use of vancomycin compared to that of surgery without it was of 0.38 (Random effects model), 0.3803 [0.2810; 0.5146], p=0.0001.

2. Which are the risks when the vancomycin powder is used?

The authors suggested that the use of vancomycin powder can increase the incidence of infection by gram-negative bacteria and seromas (since they reported collections with negative culture results in their series)[27] **(B)**.

Another study reported the use of the vancomycin to be safe regarding nephrotoxicity, ototoxicity, and rashes. However, it highlights there are studies that have shown lower fusion rates for cases of vancomycin associated with bone grafting, for high concentrations of vancomycin cause cytotoxicity over in vitro osteoblasts[13] **(B)**. In 911 cases studied, when a dose of 2 g (highest dose found in the studies – range from 500 mg to 2 g) was used, there were no reported adverse effects that could be attributed to the vancomycin powder in any of the cases. It was concluded that the vancomycin powder does not reach toxic levels, nor does it alter kidney function in patients. Therefore, it is safe to use it. The clear majority of the studies did not report any side effect to the use of intraoperative vancomycin powder at the surgical site[8] **(B)**.

TABLE 2 - DOSE OF TOPICAL VANCOMYCIN USED BY EACH STUDY

Study	Dose
O'Neil et al., 2011	1 g
Sweet et al., 2011	2 g
Pahys et al., 2013	0,5 g
Strom et al., 2013	1 g
Strom et al., 2013	1 g
Caroom et al., 2013	1 g
Kim et al., 2013	1 g
Godil et al., 2013	1 g
Tubaki et al., 2013	1 g
Martin et al., 2015	2 g
Emohare et al., 2014	1 g
Theologis et al., 2014	2 g
Martin et al., 2014	2 g
Scheverin et al. 2015	1 g every three levels
Tomov et al., 2015	1 g
Liu et al., 2015	0.5 g - 2 g
Heller et al., 2015	0.5 g - 2 g
Schroeder et al., 2016	1 g
Lee et al. 2016	1 g
Hey et al., 2016	1 g
Van Hal et al, 2017	1 g
Chotai et al, 2017	1 g

3. What is the recommended dose of vancomycin powder to be inserted in the surgical site to prevent infections in dorsal surgical approaches in the spinal column?

Out of the 22 studies, 15 used a 1 g dose of vancomycin powder, four used 2 g, and three adjusted the dose according to the extent of the surgery, ranging from 500 mg to 2 g, and only one[11] **(B)** used 500 mg as the standard dose of vancomycin powder, studying only patients who underwent posterior cervical surgery. **(Table 2)**

The dose most frequently used was 1 g. One author[21] **(B)** used 1 g of vancomycin powder for every three segments addressed.

The studies by Martin[16,19] **(B)** using a 2 g dose at the surgical site did not show any benefits regarding protection from infections.

RECOMMENDATIONS

The intraoperative use of the vancomycin power reduced the number of postoperative infections in the spinal column **(B)**.

There were no serious or unwanted side effects in the studies assessed **(B)**.

The recommended dosage is of 1 g of vancomycin power at the surgical site **(B)**.

This recommendation is mostly based on case-control studies with no evidence of significant adverse effects (Moderate quality). Future studies may influence or change the estimate of the observed effect.

APPENDIX I
Structured question

The clinical questions were structured according to the search strategy based on PICO structured questions (meaning "Patient", "Intervention", "Control", and "Outcome").

P - Patients of all ages who underwent spine surgery in any segment (cervical, thoracic, and lumbar).
I - The use of topical vancomycin power during surgery (intraoperative).
C - Patients who underwent spine surgery and did not use this antibiotic.
O - Postoperative infection rates for spine surgeries and complications with the use of vancomycin.

Methodology for evidence search

We reviewed articles from the Medline (PubMed), Embase, and Lilacs databases, with no time limit.

PubMed-Medline (07/07/2017)

"vancomycin" [MeSH Terms] OR "vancomycin" [All Fields]) AND ("powders"[MeSH Terms] OR "powders"[All Fields] OR "powder"[All Fields]) AND ("spine"[MeSH Terms] OR "spine"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]

Selection of papers

The evidence used was retrieved by the following steps elaboration of clinical question, structuring of the question, search for evidence, critical evaluation, and selection of evidence.

The studies were initially selected by title, then by summary and, lastly, by their complete text, being the last one subject to critical evaluation and the extraction of all results relating to outcomes.

Language

Only studies available in Portuguese, English, or Spanish were included.

According to publication

Only studies with texts available in its entirety were considered for critical evaluation.

The primary studies to be assessed were random studies; when these were not available, then comparative studies.

The articles returned from the search were initially assessed by their titles. The titles identified were reassessed by their abstracts, and those selected were fully evaluated. Two authors were responsible for the independent evaluation of the results and all disagreements were resolved through discussions between them. Controlled observational studies and randomized studies, both prospective and retrospective, were included. Studies with less than 20 patients were excluded.

Critical evaluation and level of evidence

With the aim of reducing biased data from systematic reviews, some instruments were used to help assess the methodological quality of each of the articles included.

Randomized clinical trials were assessed using the Cochrane tool for quality of clinical trials.

Studies such as cases and controls, and cohort studies can have their quality assessed using the New Castle-Ottawa Scale (NOS)[29]. This instrument uses an evaluation system called star system, which considers three different aspects: study selection, group comparability, and desired outcome assessment[29].

Data Analysis

The statistical analysis used the meta-analysis software "R package".

For continuous variables: mean difference and confidence interval (CI) of 95%.

Dichotomous variables: relative risk of 95% CI.

The statistical heterogeneity was assessed using the chi-squared test and I2. The fixed effects of the model were used in cases with no calculated heterogeneity.

The inconsistencies of the studies were interpreted with I2:

0% to 40% - may not be relevant,

30% to 60% - may represent heterogeneity,

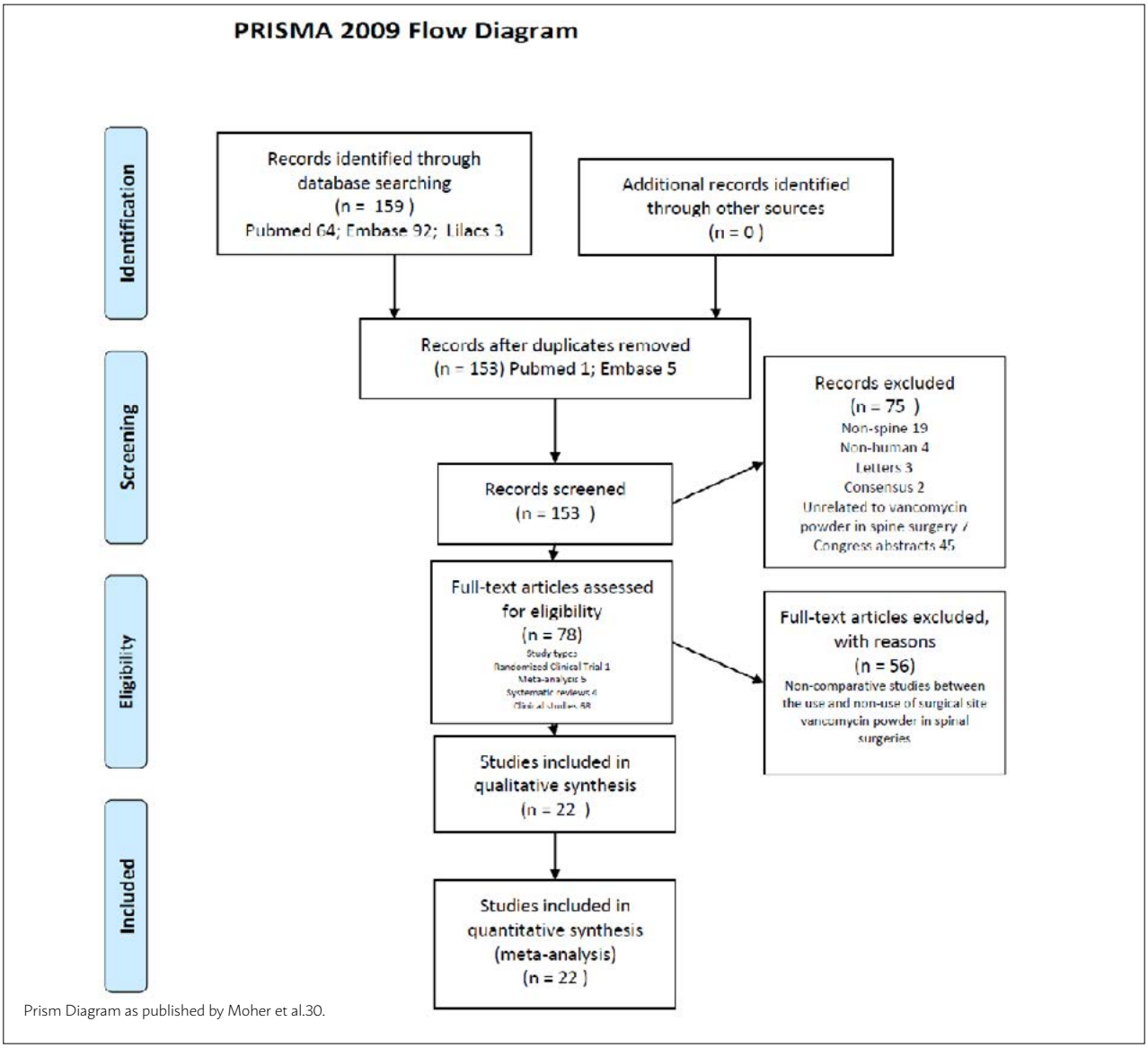
50% to 90% - may represent substantial heterogeneity, and

75% to 100% - has considerable heterogeneity.

Fixed and randomized effects were used according to the quality of inconsistencies found. Moderate and high inconsistencies were analyzed according to the random effects model.

Presentation of results

A total of 78 papers were retrieved, out of which 22 were fully assessed after our inclusion and exclusion criteria were applied. Amongst the 22 studies, we found 21 of the case-control type and one randomized clinical trial.



Prism Diagram as published by Moher et al.30.

METHODOLOGICAL QUALITY ASSESSMENT

Randomized clinical trial

Tubaki et al. published, in 2013, the only randomized clinical trial identified in this review[9].

Selection bias: The randomization was computer generated. Both groups, of use and non-use of vancomycin, did not present differences in baseline characteristics. These groups were comparable.

Performance bias: There was no attempt at a blinded grouping for treatment. Neither patients nor result evaluators were blinded. All patients had a 12-week follow up after the surgery.

Attrition bias: There were no described losses in the segment. There was no differentiation between loss of results and abandonment from the study. Patients had a follow-up long enough to assess the outcome (18 months). In the group treated with vancomycin, the infection rate was of 1.61%, and in the control group of 1.68%. These extremely low infection rates might have contributed to demonstrate the lack of effectiveness of vancomycin in these studies.

Based on the infection rates described for both samples and estimating a confidence interval of 95% and a statistical test with 80% of power, the estimated sample size necessary to reveal statistical differences would be much greater than the one studied.

NON-RANDOMIZED STUDIES (OBSERVATIONAL)

Twenty-one studies were of the case-control type, comparing infection rates in surgeries using and not using the intraoperative vancomycin power. The selection of cases and controls was considered adequate in all of them, for every patient was operated and used or did not use the antibiotic. In the comparability for infection odds (primary outcome), even though some studies used a logistic regression isolating possible confounding risk factors for the outcome, (such us age and diabetes mellitus), none of them performed an adjusted risk assessment for confounders. Regarding the exposure to the causal factor criteria, almost all studies used retrospective cohorts as comparators, with different times and samples, impairing the homogeneity of exposure to the risk of infection.

Case-control studies – New Castle-Ottawa Scale (NOS) (Table 3)

Publication bias of the studies evaluated (funnel plot):

The funnel plot reveals study asymmetry with a prevalence of studies with lower standard error (bigger sample size).

TABLE 3 – TWENTY-ONE STUDIES WITH QUALITY ASSESSMENT ACCORDING TO THE NOS CLASSIFICATION

Study	Selection	Comparability	Exposure	Details of the study
O'Neil et al., 2011	****	*	**	Patients with trauma. Posterior spinal fusions. The treatment and control groups were statically similar.
Sweet et al., 2011	****	*	**	Non-concurrent case-controls. Thoracolumbar fusions.
Caroom et al., 2013	****	*	**	Non-concurrent case-controls. The intervention group tended a bit to more complex procedures.
Godil et al., 2013	****	*	**	Not controlled for confounding factors but with no differences between samples.
Kim et al., 2013	****	*	**	Current vs. Previous. Instrumented spinal column in every level.
Pahys et al., 2013	****	*	**	Data collected and analyzed by three independent reviewers. Significant differences between the samples.
Strom et al., 2013	****	*	**	Current vs. Previous. Cases with instrumentation and cases without it. Balanced for instrumentation.
Strom et al., 2013	****	*	**	Current vs. Previous. Cases with instrumentation and cases without it.
Emohare et al., 2014	****	*	**	Grouping of patients according to surgeon recommendation or admission call. Significant differences between the samples.
Martin et al., 2014	****	*	**	Current vs. Previous. Association between infection and the vancomycin powder with and without risk adjustment.
Theologis et al., 2014	****	*	**	Current vs. Previous. Significant differences between samples
Heller et al., 2015	****	*	**	Current vs. Previous. Posterior instrumented surgeries. 8% of segment loss. Samples not balanced for age.
Liu et al., 2015	****	*	**	Current vs. Previous. Significant differences between the samples.
Martin et al., 2015	****	*	**	Current vs. Previous. Significant differences between samples.
Tomov et al., 2015	****	*	**	Current vs. Previous. Current terminology codes. Data from the US Center for Infection Prevention and Control.
Scheverin N et al. 2015	****	*	**	Vancomycin prescribed according to the preference of the surgeon. Significant differences between samples.
Hey et al., 2016	****	*	**	Significant differences between samples.
Lee et al. 2016	****	*	**	Current vs. Previous. Uni and Multivariate analysis for covariables.
Schroeder et al., 2016	****	*	**	Current vs. Previous. Significant differences between samples.
Chotai et al., 2017	****	*	**	Not controlled for confounding factors but with no differences between the samples.
Van Hal et al., 2017	****	*	**	Current vs. Previous

RECOMMENDATION

The articles were selected after a critical assessment of the level of evidence by specialists of the participant societies with the recommendation for publication of those with greater level of evidence.

The recommendations of outcomes were based on the GRADE guidelines[31].

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