REVIEW ARTICLE

Intraoperative vancomycin powder and post-operative infection after spinal surgery: a systematic review and meta-analysis

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SUMMARY

KEYWORDS: *Vancomycin. Intraoperative care/methods. Spine/surgery. Surgical wound infection/prevention & control.*

INTRODUCTION

Spinal infections after spinal surgeries are important complications that increase morbidity and even mortality, besides their economic and social impact[1-3]. Infections may lead to osteomyelitis, problems with wound healing, instrumentation failure, pain and systemic complications such as sepsis and death[2,4]. Incidence varies tremendously, from 0.5% to 15% in these cases[1,5].

Some studies suggest benefits of adding vancomycin powder into the surgical wound concomitant to conventional parenteral antibiotics prophylaxis to avoid staphylococcal infections[6,7].

The objective of this study is to evaluate the use of intraoperative vancomycin powder delivered into surgical wounds in spinal surgery to decrease post-operative spinal infections.

METHODS

A systematic literature review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[8].

Search Strategy, selection of studies and data collection

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The PICO acronym was used with the following criteria:

P – Patients – any patient who underwent spinal surgery, of any age, with or without instrumentation.

I – Intervention – patients who receive vancomycin powder into the surgical wound.

C – Control – patients who did not receive vancomycin powder into the surgical wound.

O – Outcome – post-operative infection rates in both groups

The search strategy was based on the following Mesh descriptors terms and word text: "vancomycin"; "spine"; "surgical procedures," "operative." The sources of the articles were PubMed, Embase, Central Cochrane Database and LILACS - on July 09, 2017. Articles in English, Spanish and Portuguese were revised and evaluated.

SELECTION OF STUDIES

Titles and abstracts were reviewed by three authors (AFJ, JWD, RVB). The selected titles had their full papers evaluated. Discrepancies were solved by consensus among all authors using virtual web meetings.

Types of evaluated studies: randomized trials and, if not available, controlled clinical studies evaluating the use of vancomycin powder were deemed to be evaluated.

Data extraction: Data was extracted in a specific spreadsheet according to the number of patients, infection rates, vancomycin doses, spinal procedures, and complications. The process of literature selection is illustrated in the Prisma Flow Chart Diagram (Figure 1). Methodological Quality Evaluation: For randomized trials, the risk of bias was evaluated according to the Cochrane Collaboration guidelines[9], which include random sequence generation (selection bias), allocation concealment (selection bias), blinding of the participants and personnel (performance bias), blinding of the outcomes assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias.

For the observation papers, Risks of Bias (ROB) were evaluated following the Newcastle Ottawa Scale (NOS)[10].

Individual selected studies were graded according to their level of evidence following the OXFORD level of evidence-based medicine[11].

GRADE recommendation guidelines were used to evaluate the effect of vancomycin powder in decreasing post-operative spinal infections[12].

Statistical Analysis: The software used for meta-analysis was "R" core Team (R Foundation for Statistical Computing, Vienna, Austria). Statistical heterogeneity was evaluated using the Cochran's Q test and I2. Random effect model was used in case of substantial inconsistencies.

RESULTS

The electronic search identified 64 articles on Medline, 92 on Embase and one in LILACS. After removal of duplicated articles, 151 titles were identified. Abstracts were evaluated, identifying 78 articles for the full-text evaluation. Twenty-two papers were finally analyzed. One article[13] was a randomized trial (Level 2B), and another 21 were case-control studies (Level 3B) (Table 1). Of note, the studies included different spinal levels, surgical approaches and, in the majority of them, instrumented posterior fusions[14,18-21,30,31].

Risk of Bias

Randomized trial

Tubaki et al.[13] published in 2013 the only identified randomized paper in this review.

Selection bias: Randomization was done using a computer-generated sequence. Samples with the use and non-use of vancomycin had no baseline differences in characteristics. Both groups were well comparable.

Performance bias: there was no attempt to conceal the allocation of samples for treatment. There were no Blinding of participants, personnel and outcome assessors. Wound infections were monitored during the follow-up period. All patients were followed up for at least 12 weeks from the date of surgery.

Attrition bias: there were no described losses in the final follow-up. There was no difference in outcome loss and withdrawals from the samples in this study. Patients were followed for a sufficient time to reveal the desired outcome (12 months).In the Vancomycin group infection rate was 1.61% and in the control group, 1.68%. This meager infection rate may have contributed to the lack of vancomycin effect in this trial. Along with the infection rates described above for both samples, estimating the 95% confidence interval, one statistical test with 80% power, the estimated sample size to reveal differences would

TABLE 1 - CHARACTERISTICS OF THE 22 STUDIES USED IN THE META-ANALYSIS

Author/year	Groups appraisals	Surgical site infection rate (N patients/ Infections%); Comparisons between control (non-SSVP) and treatment groups (with SSVP)	Follow–up and general considerations
1. O'Neil et al.[14], 2011	Posterior spine instrumented fusions in traumatic aliments; All spinal segments	Control group: 54/13%; Treatment group: 1 g SSVP, 56/zero (p=0.02)	Median: 25 weeks; No adverse effects
2. Sweet et al.[7], 2011	Posterior spine instrumented fusions in deformity, traumatic, neoplastic aliments; Lumbar and thoracic spinal segments	Control group: 821/2.6%; Treatment group: 2 g SSVP, 911/0.2% (p<0.0001)	Average: 2.5 years; No adverse effects
3. Pahys et al.[15], 2013	Posterior spine instrumented fusions in degenerative, deformity, traumatic, neoplastic, congenital aliments; Cervical spine	1. Control group: IV ATB, 483/1.86%; 2. Control group: IV ATB+Skin alcohol foam + drain, 323/0.3% (p=0.047); 3. Treatment group: IV ATB+ Skin alcohol foam + drain + 500 mg SSVP, 195/zero (p=0.048)	Minimum: 3 months; Risk factors: A BMI* of>30 kg/m^2 and rheumatoid arthritis had the strongest association with acute postoperative infections No adverse effects
4. Strom et al.[16], 2013	Posterior spine instrumented fusions in degenerative, infectious, traumatic, neoplastic aliments; Cervical spine, occipitocervical and cervicothoracic spinal segments	Control group: 92/10.9%; Treatment group: 1 g SSVP, 79/2.5% (p=0.0384)	Control group: Mean 4.5 years; Treatment group: Mean 2.2 years; Absence of complications; Adverse effect: pseudarthrosis: Control group 92/5.4%; Treatment group 79/5.1% (p=1.000)
5. Strom et al.[17], 2013	Posterior spine instrumented and non instrumented fusions in degenerative, infectious, traumatic, neoplastic aliments; Thoracic and lumbar spinal segments	Control group: 97/11% overall rate (non instrumented 20/10%, instrumented 77/12%, p=0.0008); Treatment group: 1 g SSVP, 156/zero overall rate (non-instrumented 68/zero, instrumented 88/zero (p=0.049)	Control group: Mean 4.5 years; Treatment group: Mean 1.9 years; Absence of complications and no adverse effects
6. Caroom et al.[18], 2013	Posterior cervical decompression Instrumented in multilevel cervical spondylotic myelopathy (CSM); Cervical spine	Control group: 72/15%; Treatment group: 1 g SSVP, 40/zero (p=0.007)	Control group: Follow-up NI; Treatment group: Minimum of 6 months, average 18 months; No adverse effects
7. Kim et al.[19], 2013	Posterior, anterior and lateral approaches instrumented in degenerative, traumatic and neoplastic aliments; All spinal segments	Control group: 40/12.5%, all in posterior approaches: Treatment group: 1 g SSVP, 34/zero (p=0.033)	Follow-up: NI; Risk factor: Elderly patients No adverse effects;
8. Godil et al.[20], 2013	Posterior cervical approach instrumented in traumatic aliments; Cervical spine	Control group: 54/13% Treatment group: 1 g SSVP, 56/zero (p=0.02)	Control and treatment groups: median 25 weeks; No adverse effects
9. Tubaki et al.[13], 2013	Open instrumented and non instrumented spine surgery; Aliment types: NI; All spinal segments	Control group: 474/1.68% Treatment group: 1 g SSVP, 433/1.61% (p>0.05)	Control and treatment groups: minimum of 12 weeks; No adverse effects
10. Martin et al.[6], 2014	Open instrumented spine surgery in deformity; Thoracolumbar and lumbar spinal segments	Control group: 150/5.3%; Treatment group: 2 g SSVP, 156/5.1% (p=0.936)	Control and treatment groups: 30 days; No adverse effects
11. Emohare et al.[21], 2014	Open instrumented and non- instrumented spine surgery; Thoracic, thoracolumbar and lumbar spinal segments	Control group: 207/NI, return-to-surgery for infection = 6.71%; Treatment group: 1 g SSVP, 96/NI, return-to-surgery = zero (p=0.0841)	Follow-up: NI; Adverse effects: NI
12.Theologis et al.[22], 2014	Open instrumented spine surgery in deformity; Thoracic, thoracolumbar and lumbar spinal segments	Control group: 64/NI, readmissions within 90 days for SSI = 10.9%; Treatment group: 2 g SSVP, 151/NI, readmissions within 90 days for SSI = 2.6% (p=0.01)	Control group: median 34 months; Treatment group: 18 months; No adverse effects
13. Martin et al.[3], 2015	Open posterior instrumented spine surgery in degenerative, deformity, neoplastic and traumatic aliments; Occipitocervi cal, cervical only, and cervicothoracic spinal segments	Control group: 174/6.9%; Treatment group: 2 g SSVP, 115/5.2% (p=0.053)	Control and treatment groups: 30 days; No adverse effects
14. Scheverin et al.[23], 2015	Open posterior instrumented spine surgery in degenerative aliments; Lumbar spine	Control group: 281/4.98%; Treatment group: 1 g SSVP, 232/1.29% (p=0.0245)	Control and treatment groups: mean 10 months; Risks for SSI: age > 65 years, obesity, prolonged surgery, surgical blood lose; No adverse effects
15. Tomov et al.[24], 2015	Open and percutaneous, anterior and posterior, instrumented and non instrumented spine surgery in deformity, degenerative, traumatic, neoplastic aliments; All spinal segments	Control group: NI; Treatment group: 1 g SSVP, NI; SSI rates were reduced by 50% after the intervention with SSVP (p=0.042)	Follow-up: NI; Risks for SSI: anemia, prior operation, vertebral fracture; Adverse effects: NI

Author/year	Groups appraisals	Surgical site infection rate (N patients/ Infections%); Comparisons between control (non-SSVP) and treatment groups (with SSVP)	Follow–up and general considerations
16. Liu et al.[25], 2015	Open posterior spine surgery in degenerative, deformity, neoplastic aliments; Cervical, thoracic, lumbar spinal segments	Control group: Non-tumor, non-SSVP, 129/7%; Tumor, non-SSVP, 25/8% (p=0.011). Treatment group: Non-tumor, 0.5 mg - 2 g SSVP, 153/0.7%; Tumor, 0.5 mg - 2 g SSVP, 27/14.8% (p=0.442).	Control and treatment groups: 3 months; Preoperative radiotherapy may contribute to the increase of SSI; No adverse effects
17. Heller et al.[26], 2015	Open posterior spine surgery in degenerative, deformity, neoplastic; traumatic aliments; Cervical, thoracic, lumbar spinal segments	Control group: 341/3.89%; Treatment group: 0.5 mg-2 g SSVP, 342/1.1%; (p=0.029)	Control and treatment groups: 90 days. Risk factors for SSI: Discharge to skilled nursing or rehabilitation facilities; No adverse effects
18.Schroeder et al.[27], 2016	Open posterior or anterior, non instrumented and instrumented cervical, thoracic, lumbar spine surgery (anterior cervical excluded); Spinal aliments: NI	Control group: 2253/1.33%; Treatment group: 1-1.5 g SSVP, 1224/0.40% (p=0.04)	Control and treatment groups: 12 months; Adverse effects: NI
19. Lee et al.[28], 2016	Open posterior lumbar spine surgery; Spinal aliments: NI (excluded traumatic)	Control group: 296/10.5%; Treatment group: 1 g SSVP, 275/5.5%	Control group: mean 11 months; Treatment group: mean 8 months; Risk factors: Diabetes mellitus, cardiovascular disease, and longer hospital stay; No adverse effects
20. Hey et al.[29], 2017	Open posterior, lateral spinal surgery; Degenerative, developmental, traumatic, infectious, neoplastic, revision; Non-instrumented and instrumented; Cervical, thoracic, lumbar	Control group: 272/6.3%; Treatment group: 1 g SSVP, 117/0,9%;	Control and treatment groups: 3 months; Adverse effects: NI
21.Van Hal et al.[30], 2017	Spinal surgery (laminectomies and arthrodesis)	Control group: 652/NI; Treatment group: SSVP dose NI, 496/5.6%	Follow-up:NI
22. Chotai et al.[31], 2017	Open posterior and anterior spinal surgery: Degenerative, deformity, neoplastic; With and without instrumentation	Control group: 1587/2.5%; Treatment group: 1 g SSVP, 1.6%	Control and treatment groups: 1 year; No adverse effects

Abbreviations: N: number of included patients; IV: intravenous; SSVP: Surgical site vancomycin powder; g: gram(s); mg: milligram(s); ATB: antibiotic; NI: Not informed; BMI: Body Mass Index; SSI: Surgical site infection

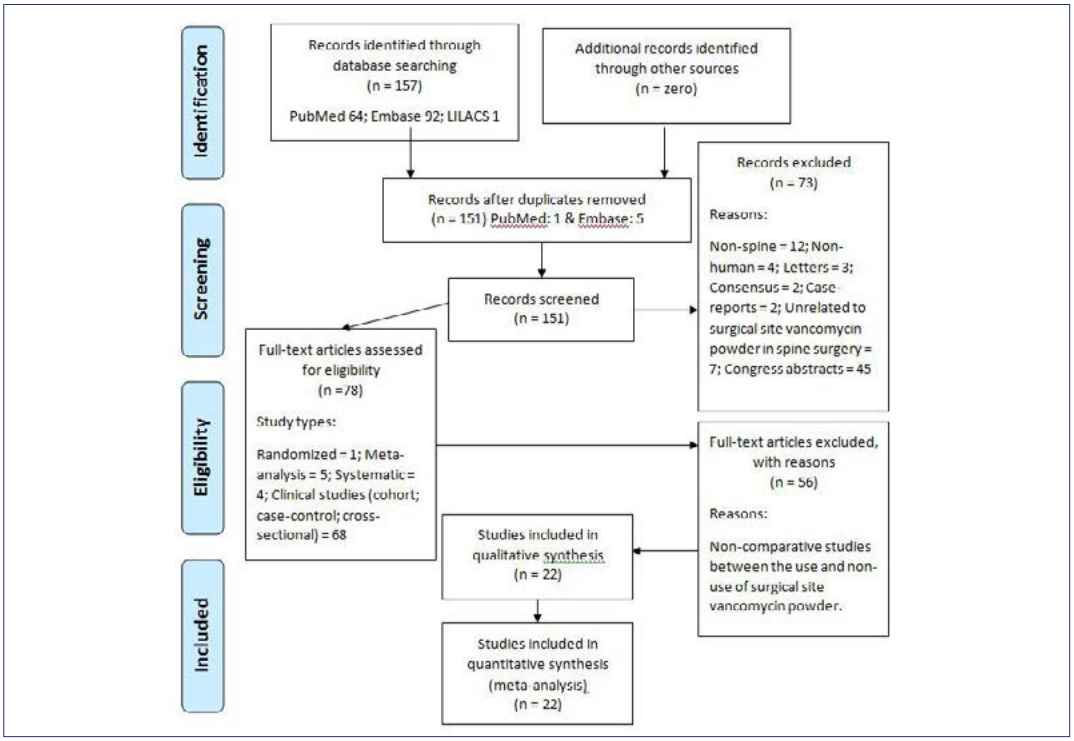

FIGURE 1

TABLE 2 - RISK OF BIAS OF CASE-CONTROL TRIALS: NEWCASTLE OTTAWA SCALE (NOS).

Study	Selection	Comparability	Exposition	
Van Hal et al.[30], 2017	****	*	**	Current vs. previous
Martin et al.[6], 2014	****	*	**	Current vs. previous. Use of propensity score adjustment.
Liu et al.[25], 2015	****	*	**	Current vs. previous. Significant differences between samples.
Tomov et al.[24], 2015	****	*	**	Current vs. previous. Data from the Healthcare Infection Management and Infection.
Martin et al.[3], 2015	****	*	**	Current vs. previous. Significant differences between samples.
Theologis et al.[22], 2014	****	*	**	Current vs. previous. Significant differences between samples.
Kim et al.[19], 2013	****	*	**	Current vs. previous.
Strom et al.[17], 2013	****	*	**	Current vs. previous. Imbalanced for instrumentation.
Heller et al.[26], 2015	****	*	**	Current vs. previous. Only 8%follow-up losses Imbalanced for age, arterial hypertension and use of hair cut.
Schroeder et al.[27], 2016	****	*	**	Current vs. previous. Significant differences between samples.
Lee et al.[28], 2016	****	*	**	Current vs. previous. Uni and multivariate analysis for covariates.
Pahys et al.[15], 2013	****	*	**	Data collected and analyzed by three independent reviewers. Significant differences between samples.
Hey et al.[29], 2017	****	*	**	Significant differences between samples
Scheverin et al.[23], 2015	****	*	**	Vancomycin indicated according to the surgeon's preference. Significant differences between samples
Godil et al.[18], 2013	****	*	**	Samples based on surgeon preferences. Non controlled for confounders but without differences between samples.
Chotai et al.[31], 2017	****	*	**	Not controlled for confounders but without differences between samples.
Carrom et al.[18], 2013	****	*	**	Current vs. previous. The intervention group trended toward slightly more complex procedures.
Sweet et al.[7], 2011	****	*	**	Current vs. previous. No significant differences between samples
Emohare et al.[21], 2014	****	*	**	Patient allocation-specific surgeon or on-call admission. Significant differences between samples.
O'Neil et al.[14], 2011	****	**	**	The treatment and control groups were statistically similar.
Strom et al.[16], 2013	****		**	Current vs. previous. No significant difference between samples.

be well above the studied sample size. Infection rates were meager and raised questions whether a study aiming to decrease infection rates should be done in this low infection rate scenario.

According to the NOS, the topic "selection" is composed of 4 components: adequate case definition, representativeness of cases selection of controls, and definition of controls. Post-operative spine infections are clinically important cases, and the review protocol admitted only papers with sufficient follow-up time, so all articles received four stars in this topic (Table 2).

In the topic "comparability," two stars may be given to each paper. Both cases and controls must be matched in the design or confounders must be adjusted for in the analysis. Although in some of the articles the authors did evaluate the importance of confounding factors, odds ratios for the exposure of interest were not adjusted in any of the articles. Thirteen papers were of current vs. previous sample of cases or non-concurrent case-control trials. Several papers had severe imbalances among cases and controls, most of them imputing greater risk of infection in the vancomycin sample. The biases described occurred more frequently in the experimental vancomycin groups, which in theory would expose the vancomycin groups to higher rates of infection, which did not occur, strengthening the revealed effect. O'Neil's paper was a concomitant case-control study without imbalance between samples and received two stars[14].

In the topic "exposure," there are two items: ascertainment of exposure and non-response rate. Only one paper described a non-response rate of only 8%. As all cases and controls were exposed to infection in surgery, and likewise, the described losses to follow-up were low, all articles received two stars.

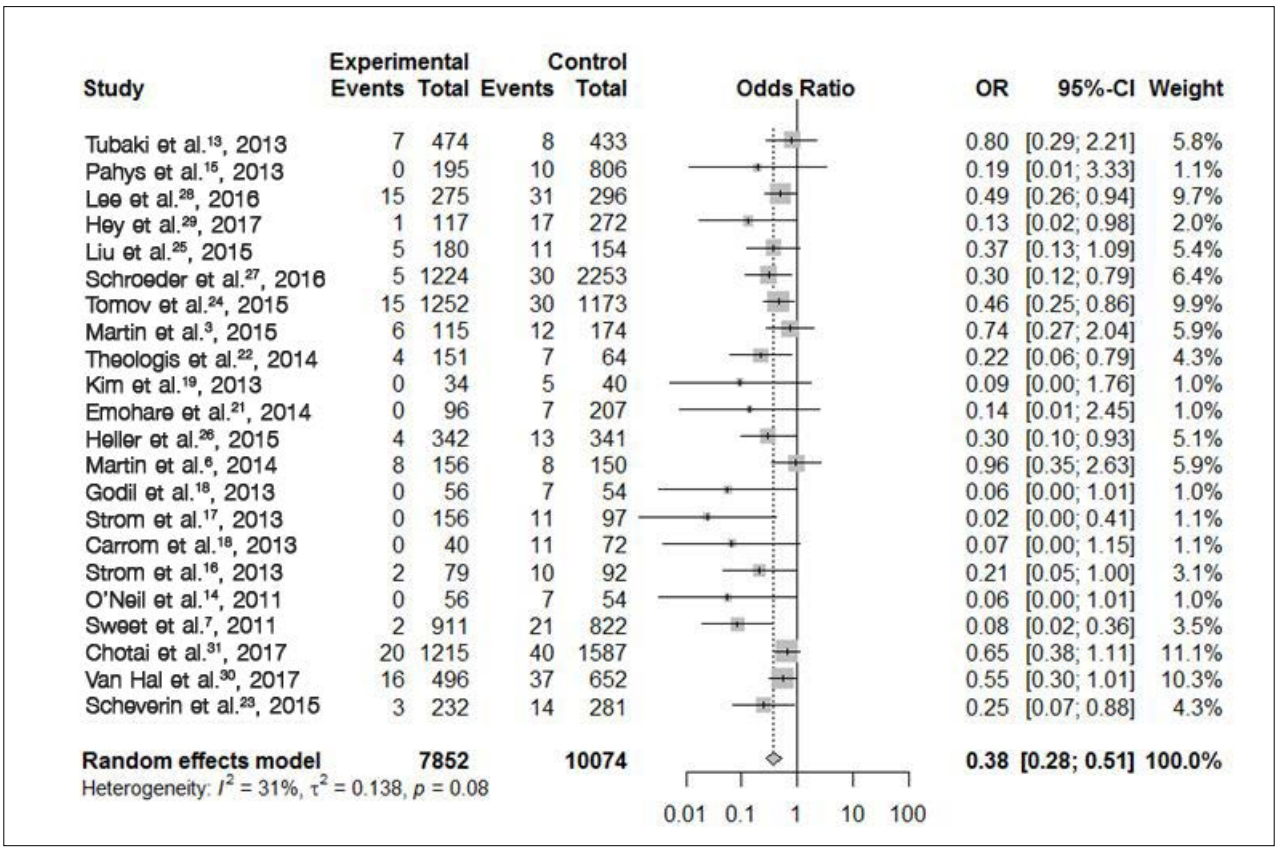

FIGURE 2

TABLE 3 – INTERVENTION EFFECTS ACCORDING TO THE IR (LOW < 2%; MEDIUM 2-4% AND HIGH ≥ 4)

Results for subgroups (random effects model):						
	k	OR	95% - CI	Q	tau^2	I^2
IR = low	3	0.4499	[0.2139; 0.9461]	2.26	0.056	11.5%
IR = medium	5	0.3612	[0.1918; 0.6800]	8.32	0.2367	51.9%
IR = high	14	0.3484	[0.2252; 0.5391]	19.99	0.2039	35.0%

Intervention Effects: Twenty-two papers were included in the pooled analysis. One article was randomized[13]. This article was evaluated alone because of its methodological superiority and level of evidence. However, this article indicated meager infection rates in both groups, even in the group that did not receive vancomycin. Each of the groups had an infection rate of less than two percent. Presented data indicated that the sample sizes needed to reveal significant differences in infection rates and would have to be larger in number. Sample sizes performances were questioned, and for this reason, we considered that this randomized study evaluated the effect of the intervention, but the outcome of interest was infrequently encountered. This way, all of the articles were pooled for analysis.

All other studies were case-control comparing the use and non-use of intraoperative topical vancomycin powder or not. Seven thousand eight hundred and fifty-two (7852) patients received vancomycin, and 10074 did not receive it. The odds ratio to develop post-operative infection was 0.38 (CI 95%: 0.28-0.51), z=-6.26, p< 0.0001, random effects model, favoring vancomycin use (Figure 2).

Subgroup analysis and intervention effects: Due to differences in infection rates (IR) among the articles, the intervention effect of vancomycin powder was tested by distributing the articles according to

the encountered IR into: low (IR <2%), medium (IR 2-4%), high (IR => 5%). Vancomycin remains effective in the 3 subgroups without significant differences (Q=0.34, p-value=0.8421) (Table 3).

To reveal the clinical benefits, results were either described with risk differences to calculate NNT (Number need to be treated to show benefits). The risk difference (random model) was: 0.0286 [-0.0383; -0.0188] (P=0.0002) favoring Vancomycin. The NNT was 35 (34.96) patients. Quantifying heterogeneity: tau^2 = 0.0003; H = 1.95 [1.58; 2.41]; I^2 = 73.7% [60.0%; 82.7%].

The characteristics of the 22 included studies used in the meta-analysis are listed in Table 1.

DISCUSSION

Post-operative spine infections represent about 22% of the costs with infectious diseases, estimated in 1 to 10 billion dollars a year[32]. After spine surgery, the incidence of surgical site infections (SSI) depends on many factors, ranging from 0.5% to 15%, with higher rates in instrumented surgeries and in deformities[33]. Staphylococcal infections (for *S. aureus* and *S. epidermidis*) are the most common agents, with an increased incidence of Methicillin-Resistant *S. aureus* (MRSA)[19,34]. These agents are not affected by commonly used cephalosporin and generally require glycopeptides antibiotics, such as vancomycin or teicoplanin. The rationale for the use of vancomycin powder into the surgical wound is that the endovenous administration has not only more systemic side effects but also an unpredictable concentration into the bone tissues, compared with elevated concentration into the wound after direct application (128 to 1457 ug/ml)[35-38].

In this review, the only prospective study did not show any advantage of the use of vancomycin powder in decreasing infection rate[13]. However, the infection rate in this study was meager (1.8% in the control group). This meager infection rate may influence the reported lack of vancomycin effect. Along with this low infection rate in both samples, considering an 80% power test and 20% type b error, the number needed to be treated to reveal a statistical difference would be much larger than those studied. Then, although this study was a randomized trial, it was evaluated along with the other observational trials.

The remaining 21 studies were case-control studies comparing the use of intraoperative topical vancomycin or its non-use. The OR to develop infection was 0.38 (CI 95%: 0.28-0.51; p< 0.0001) favoring vancomycin use.

The best quality case-control studies have been adjusted to remove the effect of confounding factors. However, ORs adjusted for confounders were not provided.

Evaluating the Vancomycin effect by the NNT, 35 treated patients are necessary to reveal benefits. Although this may be suggestive of a small effect, considering the potential damage of each infected case, potential worsening in clinical results in an infected patient and the hospitalization costs, conflicting with low cost of intraoperative vancomycin powder and almost no side effects, vancomycin effect seems robust. Besides this, unlike most randomized trials, the risk of bias in these studies contributed to a decrease in the effect of vancomycin: in cases where intraoperative antibiotics were used, they were those with the highest potential for infection. Therefore, the effect of vancomycin may even be higher than that demonstrated. According to GRADE recommendations guidelines, observational studies produce low evidence that may have an upgrade in large effects[12]. Also in line with GRADE's recommendations, it is possible to make a strong recommendation based on low-quality evidence if the desirable effects clearly outweigh undesirable effects or vice versa, or if there is evidence for at least one critical outcome from observational studies. The recommendation may change when higher quality evidence becomes available.

LIMITATIONS OF THIS META-ANALYSIS

Although the evidence of this meta-analysis suggested the benefits of adding vancomycin powder into the surgical wound in decreasing infection rates, caution is required when interpreting these results. Different patients' samples were included, as well as different procedures, in many spinal sites, although the majority of the patients were those who had posterior instrumented fusions. Moreover, our results were based on case-control studies, with a low grade of evidence, once the only randomized study had a meager rate infection rate and a relatively small number of cases to demonstrate the effects. Additionally, it is our perception that in surgeries with a very low risk of spinal infection, the benefits of adding powder vancomycin may decrease when compared with high-risk populations.

CONCLUSIONS

Based on our meta-analysis, the use of intraoperative vancomycin powder in spinal surgeries reduces post-operative spine infections with moderate evidence according to GRADE guidelines. However, this recommendation is mainly based on case-control studies with a low level of evidence. Future randomized studies with homogeneous patient populations that undergo spinal surgeries are necessary to improve the grade of recommendation as well as to select patient subgroups that may have a higher benefit with this procedure.

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PALAVRAS CHAVE: *Vancomicina. Cuidados intraoperatórios/métodos. Coluna vertebral/cirurgia. Infecção da ferida cirúrgica/prevenção & controle.*

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