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REVIEW ARTICLE

Meta-analysis of topical vancomycin powder for microbial profile in spinal surgical site infections

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Abstract

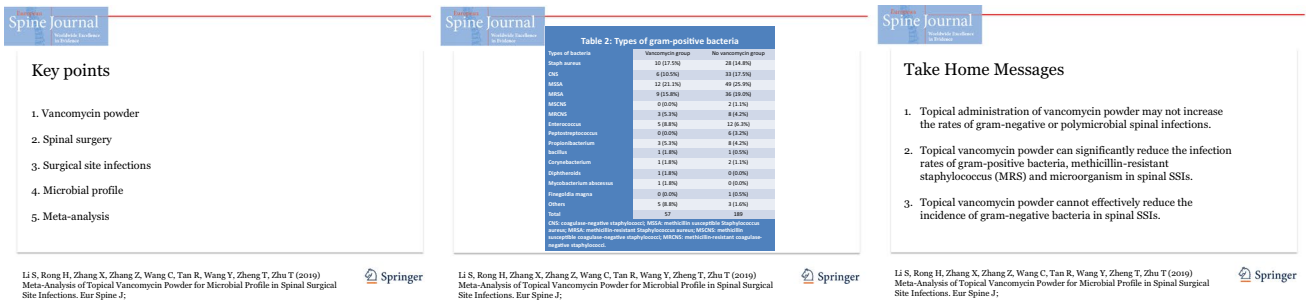
Objectives To systematically evaluate the impact of topical vancomycin powder for microbial profile in spinal surgical site infections.

Methods All available literature regarding the topical use of vancomycin powder to prevent postoperative spinal infections was retrieved from the MEDLINE, EMBASE, and Cochrane databases starting from the creation date and up until September 30, 2018.

Results A total of 21 studies involving 15,548 patients were reviewed. The combined odds ratio showed that topical use of vancomycin powder was effective for reducing the incidence of gram-positive bacterial infections in spinal surgical sites (OR 0.41, $P<0.00001$) without affecting its efficacy in the prevention of polymicrobial infections (OR 0.30, $P=0.03$). Additionally, it could significantly reduce the infection rate of methicillin-resistant staphylococcus (OR 0.34, $P<0.0001$). However, topical vancomycin powder showed no advantage for preventing gram-negative bacterial infections (OR 0.94, $P=0.75$).

Conclusions Topical administration of vancomycin powder may not increase the rates of gram-negative bacterial or polymicrobial infections in spinal surgical sites. On the contrary, it can significantly reduce the infection rates of gram-positive bacteria, methicillin-resistant staphylococcus (MRS) and microorganism. Of course, the topical vancomycin powder cannot change the rates of gram-negative bacterial infections, which may be related to the antimicrobial spectrum of vancomycin. Due to the limited number of articles included in this study, additional large-scale and high-quality studies are needed to provide more reliable clinical evidence.

Graphic abstract



Keywords Vancomycin powder · Spinal surgery · Surgical site infections · Microbial profile · Meta-analysis

Introduction

Surgical site infections (SSIs) represent a serious complication of postoperative spinal surgery and account for 21.8% of all infections associated with medical treatments [1].

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Patients who are re-admitted due to infection account for 25.1% of all unexpected hospital admissions, and orthopedic and spinal surgery patients are at the highest risk for infection-related re-admission [2].

Although the routine administration of systemic antibiotics before surgery is recommended in the Evidence-Based Clinical Guideline on Antibiotic Prophylaxis in Spine Surgery, the incidence of re-admission among orthopedic and spinal surgery patients ranges from 1 to 14% [3]. The onset of an SSI leads to a remarkable increase in hospitalization costs, a prolonged hospital stay, and in some cases, a second operation [4, 5]. Recently, topical vancomycin powder has been shown to reduce postoperative infections in spinal surgical sites [6]. However, more investigators concern that the use of vancomycin powder will change the growth of the bacterial community at surgical sites, leading to the growth of uncommon bacterial communities, especially in gram-negative bacteria and microorganism [7, 8]. Therefore, we conducted a meta-analysis of publications on the impact of topical vancomycin powder on microbial profile in spinal surgical site infections and to further explore the reliable evidence-based medical evidence.

Methods

Protocol and registration

The studies included in this meta-analysis had already been published and satisfied criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); therefore, the present study was not yet registered.

Search strategy

A systematic computer-based search of the MEDLINE, EMBASE, and COCHRANE LIBRARY databases was conducted on the literature that had been published prior to September 30, 2018. The search was performed using terms such as "spine," "Surgical Site Infection," and "Vancomycin." No language restriction was applied during the search.

Eligibility criteria

(1) Study type: randomized controlled study, cohort study, or case–control study; (2) Subjects: only patients who underwent spinal surgery; (3) Intervention and control: Both the test group and control group received standard systemic antibiotic prophylaxis. The topical vancomycin powder was administered to the test group before closing the wound, but not to the control group; and (4) Outcome endpoints: quantitative results of bacterial cultures.

Exclusion criteria

(1) Meetings, reviews, comments, letters, and case reports; (2) case reports only involving children; (3) animal experiments; (4) preoperative infections; (5) lack of control groups; and (6) obvious missing data without an explanation.

Data collection and quality assessment

Data were only extracted from published literature that included the following information: first author, year of publication, country, type of study design, study period, number of test and control groups, and the number of SSI cases. Two investigators used the Jade scale [9] to evaluate the quality of each randomized controlled trial and used the Newcastle–Ottawa scale (NOS) [10, 11] to assess the quality of observational studies.

Statistical methods

The extracted data were combined by using RevMan v5.3 software from the Cochrane Collaboration. Data heterogeneity was tested using the Q test and I^2 value. A P value > 0.1 and an I^2 value $< 50\%$ meant the heterogeneity was insignificant, and a fixed effect model was employed. A P value < 0.1 and I^2 value $> 50\%$ meant the heterogeneity was significant, and a random effect model was employed to conduct a subgroup analysis. For dichotomous variables, the effect size was combined based on the odds ratio and 95% confidence interval. The types of bacteria would be listed in detail.

Results

Search results

A total of 449 articles (134 from Pubmed, 287 from EMBASE, and 28 from the Cochrane Library) were retrieved. A total of 423 articles were excluded after deduplication, reading the title and abstract, and reading the full text. During a detailed re-assessment of the remaining 26 articles, it was found that outcome indicators was absent in five studies. Finally, 21 studies were included in the meta-analysis (Fig. 1).

Study characteristics

Twenty-one studies involving 15,548 patients were included, of which two randomized controlled trials

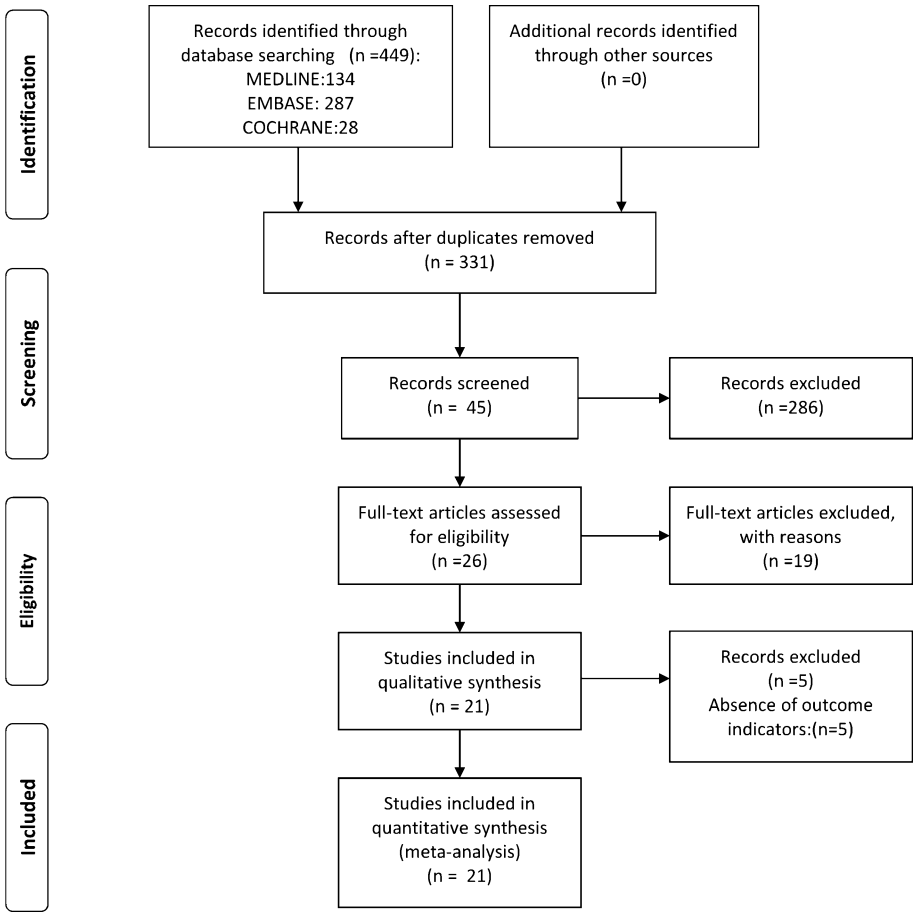

Fig. 1 Flow diagram of search strategy

(RCTs) were assessed with the Jadad scale and scored as 3 points. Two observational studies were evaluated with the NOS scale and scored as ≥ 5 stars (Table 1).

Results of the meta-analysis

Impact of topical vancomycin powder on gram-positive bacteria in spinal SSIs

The combined OR value of the studies in which gram-positive bacteria was cultured revealed insignificant heterogeneity ($P = 0.16$, $I^2 = 25\%$). In the fixed effects model, the results showed that topical vancomycin powder could effectively reduce the rates of gram-positive bacterial infections after spinal surgery when compared with the control group, and the difference between the groups was statistically significant (OR 0.41, 95% CI 0.31–0.55; $P < 0.00001$, Fig. 2). However, *Staph aureus*, coagulase-negative staphylococci (CNS), methicillin-susceptible *Staphylococcus aureus* (MSSA), and methicillin-resistant *Staphylococcus aureus* (MRSA) were the most common gram-positive bacteria in both groups (Table 2).

Impact of topical vancomycin powder on gram-negative bacteria in spinal SSIs

Our analysis was conducted on the studies in which terms gram-negative bacteria was cultured. The results revealed that topical vancomycin powder could not effectively reduce the incidence of gram-negative bacterial infections after spinal surgery when compared with the control group, as the difference between the groups was not statistically significant (OR 0.94, 95% CI 0.63–1.39; $P = 0.75$, $I^2 = 25\%$, Fig. 3). Escherichia coli (15.0% vs 26.3%) and Pseudomonas (17.5% vs 22.8%) were the most common gram-negative bacteria in both experimental group and control group, but a case of Acinetobacter baumannii was cultured in control group (Table 3).

Impact of topical vancomycin powder on polymicrobial spinal infections

In the studies that specified polymicrobial infections clearly, only five studies involving 3722 patients were found to be eligible for inclusion. The combined effect size revealed that topical vancomycin powder could effectively

Table 1 Patient characteristics and quality of included studies

Author	Country	Study design	Quality score	Study period	Dosage	Vancomycin powder			No vancomycin		
						Size	Male	Age	Size	Male	Age
Horii et al. [18]	Japan	Multicenter retrospective cohort study	NOS:7	2012.7–2014.12	1 g/2 g	694	326	68.5	2165	999	65
Mirzashahi et al. [19]	Iran	RCT	Jadad:3	2014.5–2015.9	1 g/2 g	193	NR	NR	187	NR	NR
Sono et al. [20]	Japan	Retrospective cohort study	NOS:6	2004.1–2016.6	2 g	286	132	61.9	199	85	61.0
Chotai et al. [21]	USA	Retrospective cohort study	NOS:8	2010.11–2014.7	1 g	1215	NR	NR	1587	NR	NR
Hey et al. [22]	Singapore	Retrospective cohort study	NOS:7	2012.1–2013.12	1 g	117	51	45	272	146	48
Hida et al. [23]	Japan	Retrospective cohort study	NOS:7	2014.8–2016.4	0.5–1 g	81	36	48.4	93	43	50.3
Van Hal et al. [24]	USA	Retrospective cohort study	NOS:5	2010.7–2013.8	1 g	496	NR	NR	652	NR	NR
Gaviola et al. [25]	USA	Retrospective cohort study	NOS:5	2010.1–2014.7	2 g	116	65	62	210	119	55
Schroeder et al. [26]	USA	Retrospective cohort study	NOS:5	2012.6–2013.6	1 g–1.5 g	1224	577	56.3	2253	1053	57.1
Heller et al. [27]	USA	A retrospective historical cohort design	NOS:7	2015.4–2011.9	0.5–2 g	342	155	55.3	341	168	49.1
Martin et al. [28]	USA	Retrospective cohort study	NOS:8	2011.1–2013.7	2 g	115	58	62.3	174	91	57.6
Suh et al. [29]	Korea	Retrospective cohort study	NOS:7	2006.2–2012.8	2 g	43	15	63.2	43	4	67.1
Hill et al. [30]	USA	Retrospective cohort study	NOS:5	2010.7–2012.7	1–2 g	150	80	54.14	150	67	58.33
Martin et al. [31]	USA	Retrospective cohort study	NOS:7	2011.1–2013.4	2 g	156	49	63.4	150	49	62.7
Theologis et al. [32]	USA	Retrospective cohort study	NOS:5	2008.1–2012.6	2 g	151	48	62.4	64	29	60.0
Caroom et al. [33]	USA	Retrospective cohort study	NOS:7	2003–2011	1 g	40	NR	59.8	72	NR	56.4
Kim et al. [34]	Korea	Retrospective cohort study	NOS:5	2012.7–2012.12	1 g	34	21	57.88	40	17	60.05
Strom et al. [13]	USA	Retrospective cohort study	NOS:7	2007.1–2011.12	1 g	156	89	63	97	52	64
Strom et al. [14]	USA	Retrospective cohort study	NOS:7	2007–2011	1 g	79	45	60	92	55	60
Tubaki et al. [35]	India	RCT	Jadad:3	2011.6–2012.12	1 g	433	235	44.3	474	274	46.6
O'Neill et al. [36]	USA	Retrospective cohort study	NOS:8	2008.1–2009.12	1 g	56	35	43	54	35	45

RCT randomized controlled trial, *NR* not reported

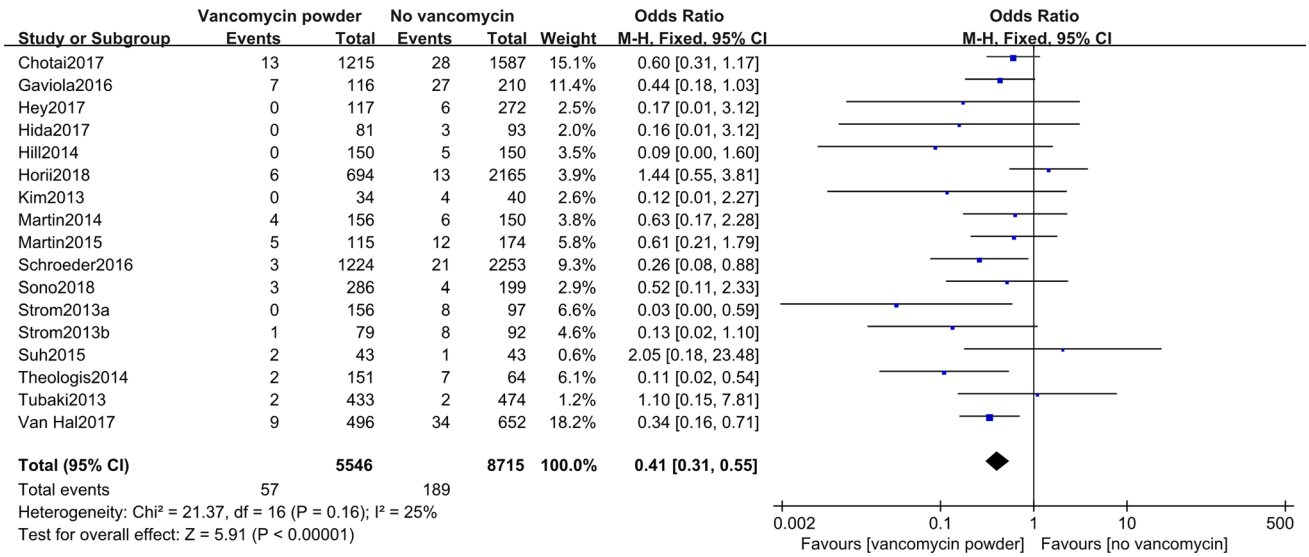

Fig. 2 Forest plot of gram-positive bacterial infections

Table 2 Types of gram-positive bacteria

Types of bacteria	Vancomycin group	No vancomycin group
Staph aureus	10 (17.5%)	28 (14.8%)
CNS	6 (10.5%)	33 (17.5%)
MSSA	12 (21.1%)	49 (25.9%)
MRSA	9 (15.8%)	36 (19.0%)
MSCNS	0 (0.0%)	2 (1.1%)
MRCNS	3 (5.3%)	8 (4.2%)
Enterococcus	5 (8.8%)	12 (6.3%)
Peptostreptococcus	0 (0.0%)	6 (3.2%)
Propionibacterium	3 (5.3%)	8 (4.2%)
Bacillus	1 (1.8%)	1 (0.5%)
Corynebacterium	1 (1.8%)	2 (1.1%)
Diphtheroids	1 (1.8%)	0 (0.0%)
Mycobacterium Abscessus	1 (1.8%)	0 (0.0%)
Finegoldia magna	0 (0.0%)	1 (0.5%)
Others	5 (8.8%)	3 (1.6%)
Total	57 (100%)	189 (100%)

CNS coagulase-negative staphylococci, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSCNS* methicillin-susceptible coagulase-negative staphylococci, *MRCNS* methicillin-resistant coagulase-negative staphylococci

reduce the incidence of polymicrobial spinal infections when compared with the control group, as the difference between the groups was statistically significant (OR 0.30, 95% CI 0.10–0.92; $P = 0.03$, $I^2 = 0\%$, Fig. 4). Specific species of bacteria had been shown in Table 4.

Impact of topical vancomycin powder on methicillin-resistant bacteria in spinal SSIs

Methicillin-resistant bacterial infections are the most serious spinal SSIs. Our analysis examined the impact of topical vancomycin powder on methicillin-resistant bacteria in spinal SSIs. The results showed that topical vancomycin powder could help to reduce the incidence of methicillin-resistant bacterial infections (OR 0.34, 95% CI 0.20–0.58; $P < 0.0001$, $I^2 = 0\%$, Fig. 5), and the effect was statistically significant (Table 5).

Sensitivity analysis

A sensitivity analysis was performed to exclude any single study by using the one-by-one exclusion method. After combining the OR values of the remaining studies, no individual study was found to have a significant impact on the final results.

Discussion

Infection at the surgical site is a serious complication of spinal surgery. As noted in the North American Spine Society's (NASS) Evidence-Based Clinical Guideline on Antibiotic Prophylaxis in Spine Surgery [12], the incidence rate of spinal SSIs in spinal surgeries when only antibiotics are administered is 0.7% to 10% and can reach 2.0–10% in patients with concomitant diseases such as diabetes. In 2011, Sweet et al. [6] reported that vancomycin powder significantly reduced the incidence of spinal SSIs. Furthermore, when vancomycin was applied to spinal surgery wounds at

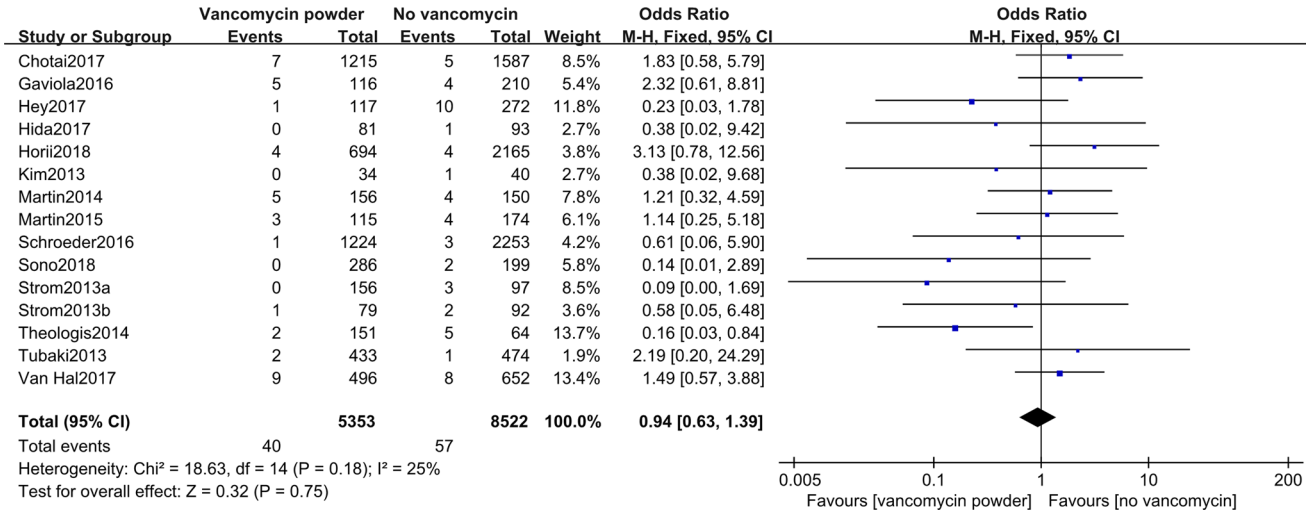

Fig. 3 Forest plot of gram-negative bacterial infections

Table 3 Types of gram-negative bacteria

Types of bacteria	Vancomycin group	No vancomycin group
Escherichia coli	6 (15.0%)	15 (26.3%)
Enterobacter	5 (12.5%)	3 (5.3%)
Bacteroides fragilis	1 (2.5%)	0 (0.0%)
Pseudomonas	7 (17.5%)	13 (22.8%)
Proteus	3 (7.5%)	6 (10.5%)
Morganella morganii	1 (2.5%)	3 (5.3%)
Klebsiella	4 (10.0%	3 (5.3%)
Serratia marcescens	2 (5.0%)	3 (5.3%)
Acinetobacter Baumannii	0 (0.0%)	1 (1.8%)
Citrobacter freundii	2 (5.0%)	0 (0.0%)
Anaerobic Gram-negative bacilli	1 (2.5%)	0 (0.0%)
Others	8 (20.0%)	10 (17.5%)
Total	40 (100%)	57 (100%)

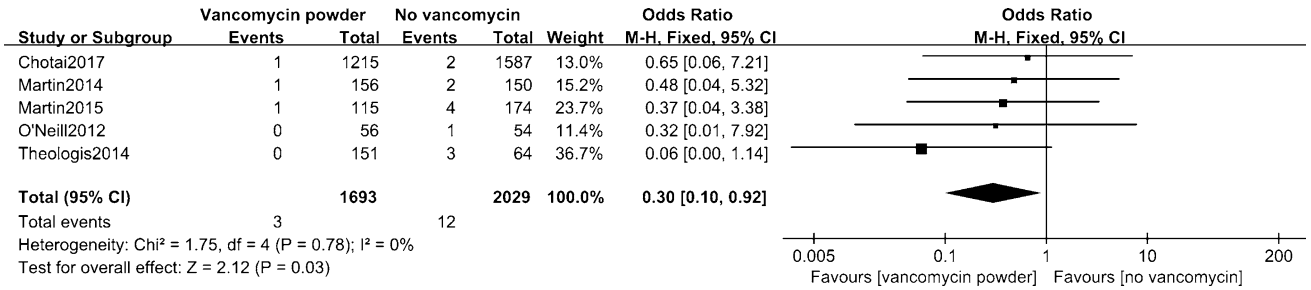

Fig. 4 Forest plot of polymicrobial spinal infections

concentrations 1000-fold higher than the mean inhibitory concentration (MIC) for MRSA and coagulation-negative *Staphylococcus aureus*, it did not cause significant adverse reactions when compared to reactions that occurred in a control group. Those results were also subsequently confirmed by Strom et al. [13, 14]. For these reasons, the current guidelines suggest that topical vancomycin powder can be used in addition to intravenous antibiotics in surgical patients with comorbidities and those undergoing complex spinal surgeries.

Table 4 Types of bacteria in polymicrobial infections

Vancomycin group ($n=3$)	No vancomycin group
1. Mixed anaerobic and aerobic × 1	1. MRSA; Enterobacter aerogenes × 1
2. Klebsiella pneumoniae; Citrobacter freundii × 1	2. Enterococcus; Pseudomonas aeruginosa
3. Enterobacter cloacae; Morganella morganii; Pseudomonas aeruginosa × 1	3. Coagulase-negative staphylococci; Propionibacterium × 1
	4. Coagulase-negative staphylococci; Escherichia coli × 1
	5. Coagulase-negative staphylococci; Serratia marcescens × 1
	6. Peptostreptococcus; Propionibacterium × 1
	7. MRSA; Pseudomonas mirabilis × 1
	8. Staphylococcus epidermidis; Proteus mirabilis; Escherichia coli × 1
	9. Proteus mirabilis; Enterobacter cloacae × 1
	10. Not specified × 3

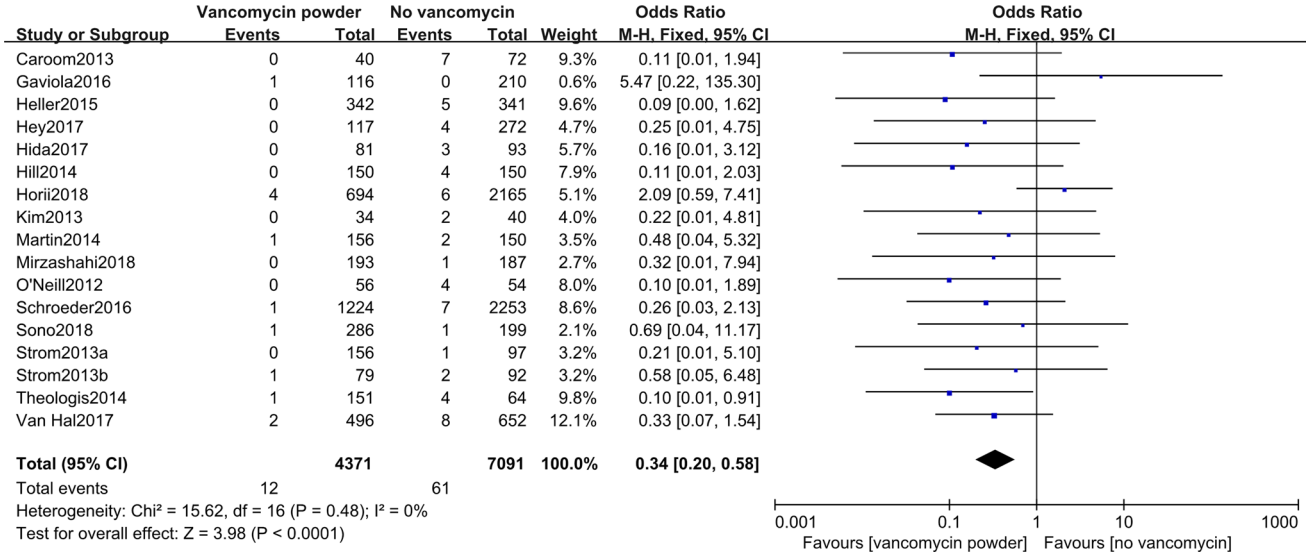

Fig. 5 Forest plot of methicillin-resistant bacterial infections

Table 5 Types of methicillin-resistant bacteria

Types of bacteria	Vancomycin group	No vancomycin group
MRSA	9 (75.0%)	51 (83.6%)
MRCNS	3 (25.0%)	10 (16.4%)
Total	12 (100.0%)	61 (100.0%)

MRSA methicillin-resistant *Staphylococcus aureus*; *MRCNS* methicillin-resistant coagulase-negative staphylococci; *MRSE* methicillin-resistant staphylococcus epidermidis

More investigators were concerned that topical vancomycin powder might increase the incidence of gram-negative bacterial and polymicrobial spinal infections [7, 8]. However, Our meta-analysis of numerous studies showed that topical vancomycin powder could reduce the incidence of gram-positive bacterial infections after spinal surgery (OR 0.41, $P<0.00001$). In addition, it could significantly reduce the infection rates of methicillin-resistant staphylococcus (OR 0.34, $P<0.0001$) and microorganism (OR 0.30, $P=0.03$), which was contrary to the results of the most current reports.

The results of this meta-analysis are attributed to the antimicrobial spectrum of vancomycin, which is effective against gram-positive bacteria and methicillin-resistant staphylococcus by inhibiting the synthesis of cell walls, so topical vancomycin powder can significantly reduce the infection rates of gram-positive bacteria and methicillin-resistant staphylococcus [15–17]. Due to vancomycin invalid of gram-negative bacteria, topical vancomycin powder will not effectively reduce the incidence of gram-negative bacteria in spinal SSIs. In topical vancomycin powder group, topical use of vancomycin powder decreasing rates of G+ bacterial infections may increase the proportion of G− bacteria within the surgical wound, but not necessarily increases the rate of G− infections. Participants in the whole test cases, the topical use of vancomycin powder or not, revealed no significant impact on the rates of gram-negative bacterial infections (OR 0.94, $P=0.75$).

Types of gram-positive bacteria, gram-negative bacteria, and various microorganisms were summarized in detail. Due to the differences of microflora shown in forest plots, we only summarized the types and proportion of bacteria in tables. *Staphylococcus aureus* was still the most common gram-positive bacteria, regardless of the use of vancomycin powder or not. In vancomycin powder group, *Staphylococcus aureus* accounted for 54.4% (including *Staph aureus* 17.5%, MSSA 21.1%, and MRSA 15.8%) and coagulase-negative staphylococci 15.8% (including CNS 10.5% and MRCNS 5.3%). In the control group, *Staphylococcus aureus* accounted for 59.7% (including *Staph aureus* 14.8%, MSSA 25.9%, and MRSA 19.0%).

Two RCT studies were included in this meta-analysis. Both RCT studies received a score of 3 points on the Jadad scale, and the remaining 19 observational studies received scores ranging from 5 to 8 on the NOS scale. In this sense, our study provides some degree of guidance for clinical practitioners. However, the limitations of this meta-analysis cannot be ignored. Only two RCT studies were included, and the total sample size was small. Additionally, differences in study populations, comorbidities, surgical methods, spinal segments, and preoperative skin preparation among the various studies led to considerable heterogeneity. Additional high-quality randomized controlled trials with large sample sizes are needed to demonstrate the efficacy of topical vancomycin powder for microbial profile in spinal surgical sites.

Conclusions

Topical administration of vancomycin powder may not increase the rates of gram-negative bacterial or polymicrobial spinal infections. On the contrary, it can significantly reduce the infection rates of gram-positive bacteria, methicillin-resistant staphylococcus (MRS), and microorganism. Of course, the topical vancomycin powder cannot change the rates of gram-negative bacterial infections, which may be related to the antimicrobial spectrum of vancomycin. However, additional large-scale, high-quality studies are needed to provide more reliable clinical evidence concerning the prophylactic value of vancomycin powder.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest or funding sources in the article.

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