Systematic Review

Efficacy of Intrawound Treatments to Prevent Surgical Site Infection after Spine Surgery: A Systematic Review and Network Meta-analysis

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Background: Intrawound treatments have been reported to have favorable efficacy for preventing surgical site infection (SSI); however, the best strategy remains unknown.

Objective: The aim of this systematic review and network meta-analysis was to evaluate the efficacy of intrawound treatments to prevent SSI after spine surgery.

Study Design: A systematic review and network meta-analysis.

Methods: We searched the Cochrane Library, EMbase, PubMed, Chinese Science and Technology Periodical Database (VIP), China National Knowledge Infrastructure (CNKI), and Wanfang Data from the date of inception to March 2, 2020. The randomized controlled trials (RCTs) and cohort studies were identified and extracted by 2 reviewers independently. We performed a traditional pairwise meta-analysis to evaluate overall efficacy of intrawound treatments. Meanwhile, a network meta-analysis was performed to compare and rank the treatment efficacy using frequentist approach.

Results: Thirty-three publications (6 RCTs and 27 retrospective cohort studies) were included, involving 22,763 patients. For pairwise meta-analysis, the combined results showed that the intrawound treatment had a significantly lower SSI rate than the control group (CG) (odds ratio [OR] = 0.41; 95% confidence interval [CI], 0.31–0.55). For network meta-analysis, the treatment of vancomycin (VA) (OR = 0.53; 95% CI, 0.39-0.71), povidone-iodine (PI) (OR = 0.10; 95% CI, 0.04 - 0.23), and vancomycin + povidone-iodine (VA+PI) (OR = 0.25; 95% CI, 0.11-0.58) were found to be significantly more efficacious than CG on reduction of SSI rate. PI ranked first on reducing SSI, followed by PI+HP, VA+PI, gentamicin (GM), VA, and hydrogen peroxide (HP); CG ranked last.

Limitations: Firstly, only 6 RCTs are included in this systematic review. Retrospective cohort studies tend to exaggerate the real results, although most of them are high-quality according to the Newcastle-Ottawa Quality Assessment Scale (NOQAS). More high-quality RCTs need to be included to obtain convincing conclusions. Secondly, the population of this study involves both adult and pediatric cohorts, patients with tumor, congenital disease, or degenerative disease. There is no subgroup analysis for ages and type of diseases, which might have influence on the overall pooled analysis. Thirdly, we define the application of saline solution and no intrawound treatment as the control group, which might ignore their heterogeneity. Fourthly, follow-up periods are variable and the sample size of HP is small. Finally, additional research is needed to compare the complications of different treatments and the benefits of various dosages.

Conclusion: We found that VA and PI show promising results on reducing SSI. PI is recommended as the most efficacious intrawound treatment to prevent SSI after spine surgery.

Key words: Intrawound treatments, network meta-analysis, spine, surgery, surgical site infection.

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Surgical site infection (SSI) following spine surgery is one of the most frequent and potentially devastating complications. The prevalence of SSI after spine surgery has been found to range from 2-13% (1,2). Although systemic prevention strategies have been applied to clinical work, SSI remains a significant concern, which results in high morbidity, mortality, and health care expenditure (3). Patient-related risk factors, including diabetes, anemia, hypertension, obesity, urinary tract infection, smoking, alcohol abuse, advanced age, and steroid use contribute to the development of infection (4,5). Long operative time, high blood loss and use of instrumentation are also associated with a higher SSI rate (6). Bacterial culture indicates that staphylococcus aureus is the most frequent pathogen, accounting for nearly 50% of all infection, followed by staphylococcus epidermidis and gram-negative bacteria (7). The clinical symptoms of SSI, which mostly occur in the first 3 months after surgery, include pain, fever, wound erythema, localized abscess, or increased wound drainage (8,9). Patients with SSI may suffer from long-term systemic antibiotics, prolonged hospital stays, and multiple debridement operations (10). Moreover, those patients could experience worse conditions, such as pseudoarthrosis, permanent disability, sepsis, and death (9).

Preventive strategies for reducing SSI are urgently needed due to the deleterious impacts of this complication. Three main phases consisting of preoperative, intraoperative and postoperative preventive measures have gained the attention of surgeons. Optimizing risk factors, including hyperglycemic states, smoking, alcohol abuse, and obesity management can reduce the risk of SSI (11). Aseptic surgical techniques are the fundamental methods to reduce SSI. Skin antisepsis and prophylactic antibiotic therapies have been widely accepted in orthopedic surgery (12). A study of 4,547 surgeries demonstrated that preoperative chlorhexidine showering was associated with significantly reduced incidence of infection after spine surgery (13). Meanwhile, nasal decontamination, using antiseptic dressings, using antibiotic-impregnated sutures and avoiding C-arm pollution have been proven to be effective (14).

In recent years, surgeons have shown increased interest in intrawound treatments. It is reported that intrawound applications of gentamicin (GM), vancomycin (VA), povidone-iodine (PI), and hydrogen peroxide (HP) have favorable efficacy for preventing SSI (15-17). The combination of treatments vancomycin + povidone-iodine (VA+PI) and povidone-iodine + hydrogen peroxide (PI+HP) have also been explored to reduce SSI (18,19). Although these treatment options are all available for reducing SSI, the best strategy remains unknown.

Network meta-analysis as a statistical tool allows the comparison of the relative effectiveness among all intrawound treatments (20). Even if there is a lack of direct comparison in one trial, a comparison between 2 treatments is possible through another common comparator (21). This study aimed to investigate the efficacy of intrawound treatments to prevent SSI after spine surgery. We undertook a traditional, pairwise meta-analysis to demonstrate whether a treatment was better than the control group (CG), who were given no intrawound treatment or saline solution. Meanwhile, a network meta-analysis was performed to compare and rank the efficacy of different intrawound treatments (VA, PI, VA+PI, PI+HP, HP, GM, CG).

Methods

Protocol and Guidance

This systematic review and network meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis (22). The detailed protocol was available in PROSPERO with registration number: CRD42020173672.

Search Strategy

The electronic databases, including the Cochrane Library, EMbase, PubMed, Chinese Science and Technology Periodical Database (VIP), China National Knowledge Infrastructure (CNKI), and Wanfang Data were searched for relevant studies. A variety of keyword combinations of and MeSH terms including, "spine," "surgery," "intrawound," "vancomycin," "gentamicin," "povidone-iodine," "hydrogen peroxide," and "infection," were performed. Retrieval time was from the date of inception to March 2, 2020. We also manually traced the references included in the literature to obtain additional relevant literature. No language restrictions were imposed on the literature search.

Selection of Research Studies

We included randomized controlled trials (RCTs) and cohort studies where intrawound treatments for postoperative prophylaxis of surgical site infection were involved. Studies were selected based on the following criteria: 1) any patients who had undergone spine surgeries, regardless of age, gender, and whether

combined with other diseases; 2) the observation group used intrawound treatments of VA, GM, HP, PI, or combination of 2 treatments; 3) the study reported rates of SSI which included deep wound infection and superficial wound infection. Exclusion criteria were as follows: 1) patients who had previous SSI or current infection; 2) lack of control groups or no available data; 3) duplicate reports of earlier trials; 4) animal experiments, case reports, conference reports, reviews, meta-analyses, letters or comments; 5) full article was unavailable to obtain.

Data Extraction

Two researchers (LL and SC) independently examined all titles and abstracts to extract the information. Full texts were obtained and further screened according to the inclusion criteria. Any discrepancies between the 2 reviewers were resolved by discussion with a third reviewer (ZK). The following data items were extracted from eligible studies: the basic information of studies (first author's name, publication time, country, design), baseline characteristics of patients (type of operation, sample size, follow-up duration, and nature of SSI), intervention measures, and outcome indicators.

Quality Assessment

For RCTs, we used the Cochrane Collaborations tool to assess risk of bias (23). The evaluation was assessed on 7 criteria: 1) random sequence generation, 2) allocation concealment, 3) performance bias, 4) detection bias, 5) incomplete outcome data, 6) selective reporting, and 7) other bias. Each of the methodological domains was graded as "low risk," "high risk," or "unclear." The Cochrane Collaborations tool was performed in the Review Manager (RevMan) 5.2 software. The Newcastle-Ottawa Quality Assessment Scale (NOQAS) was used to assess the quality of non-RCT studies (24). This tool evaluated observational studies based on the quality of selection, comparability and outcome. The scale of NOQAS had a maximum of 9 stars, while a study could be awarded 1 star for each numbered item. Two reviewers independently assessed the quality of the included studies. Disagreements regarding the results of quality assessment were resolved by discussion and consultation with a third reviewer.

Statistical Analysis

In this study, data analyses were conducted in STATA software (version 14; STATA Corporation, College Station, TX, USA). The results of dichotomous data (rates of SSI) were analyzed using the odds radio (OR) measure with 95% confidence intervals (CIs). Firstly, we performed a pairwise meta-analysis to produce forest plots of direct comparisons. Heterogeneity between studies was assessed using the I^2 statistic, with values > 50% demonstrating substantial heterogeneity (25). We utilized the random-effects method considering the possibility of heterogeneity within the evaluated intervention groups. To resolve the heterogeneity, subgroup analysis was performed as per the interventions being compared. The sensitivity analysis was performed by excluding studies with high risk of bias in pairwise meta-analysis. Secondly, a network meta-analysis was performed using the frequentist framework random-effects model. Network meta-analysis could merge direct evidence and indirect evidence simultaneously and rank all treatments for the studied outcomes (26). A network evidence plot was produced to provide a visual summary of the comparison of different therapies. Testing the consistency between the direct and indirect evidence was statistically performed using global and local inconsistency tests. The global inconsistency showed significant inconsistency when a P value < 0.05 was present (27). The local inconsistency of the network was assessed through a loop-specific approach. Inconsistent loops suggested no significant inconsistency if the 95% CI of the inconsistency factor (IF) reached zero (21). Additionally, if there were any relevant sources of bias, we conducted sensitivity analyses. Relative rankings of interventions for the outcomes were estimated as the surface under the cumulative ranking curves (SUCRA), ranging from 0 to 100% (26,28). Higher SUCRA scores represented better results for the respective intervention. Furthermore, we generated a funnel plot to present publication bias for all available treatments (29). There were significant differences between the 2 groups with $P < 0.05$.

Results

Identification of the Relevant Studies

We performed the searches in the Cochrane Library, EMbase, PubMed, Chinese Science and Technology Periodical Database (VIP), China National Knowledge Infrastructure (CNKI), and Wanfang Data. Through our search we identified 1,051 studies initially. Five studies were searched by tracing the references included in the literature. Eight hundred twenty-eight studies were screened after removal of duplicates. After screening the titles and abstracts, the remaining 92 studies were

further screened by analysis of full text. Fifty-nine studies were excluded for various reasons: lack of control groups (5), no available data (12), systematic review (9), meta-analysis (12), duplicate reports of earlier trials (14), conference reports (2), or full article was unavailable (5). Finally, 33 studies were eligible for our analysis. Figure 1 shows the PRISMA flow diagram of the search strategy and selection process.

Characteristics of the Included Trials

The baseline characteristics of 33 eligible publications were presented in Table 1 (15,17-19,30-58). A total of 22,763 patients were identified in this analysis with sample sizes varying from 50 to 2,895. Thirty-one of the 33 studies were 2-arm trials, while 2 studies were 3-arm trials. Overall, 6 studies were RCTs and 27 were retrospective cohort studies. The main analysis comprised 7 groups (6 active treatments and 1 CG): 20 VA, 7 PI, 1 HP, 4 VA+PI, 1 PI+HP, 3 GM, and 32 CG. The network evidence plot of treated comparisons was presented in Fig. 2 and the most common comparisons were between VA and CG, followed by PI versus CG, and VA+PI versus CG.

Quality Assessment

Figure 3 represents the quality assessment of the RCTs and Table 2 summarizes the NOQAS of the retrospective cohort studies. Among the 6 RCTs, 4 trials were assessed as "low risk" using a computer or table of random numbers. Only 1 trial mentioned the blinding method and allocation concealment and 5 trials were ranked as "unclear risk." All studies were assessed as "low risk" of attrition bias and selective reporting bias. For the 27 retrospective cohort studies, 25 studies were high quality studies with scores ≥ 6. The remaining 2 studies were judged as low quality of 5 scores.

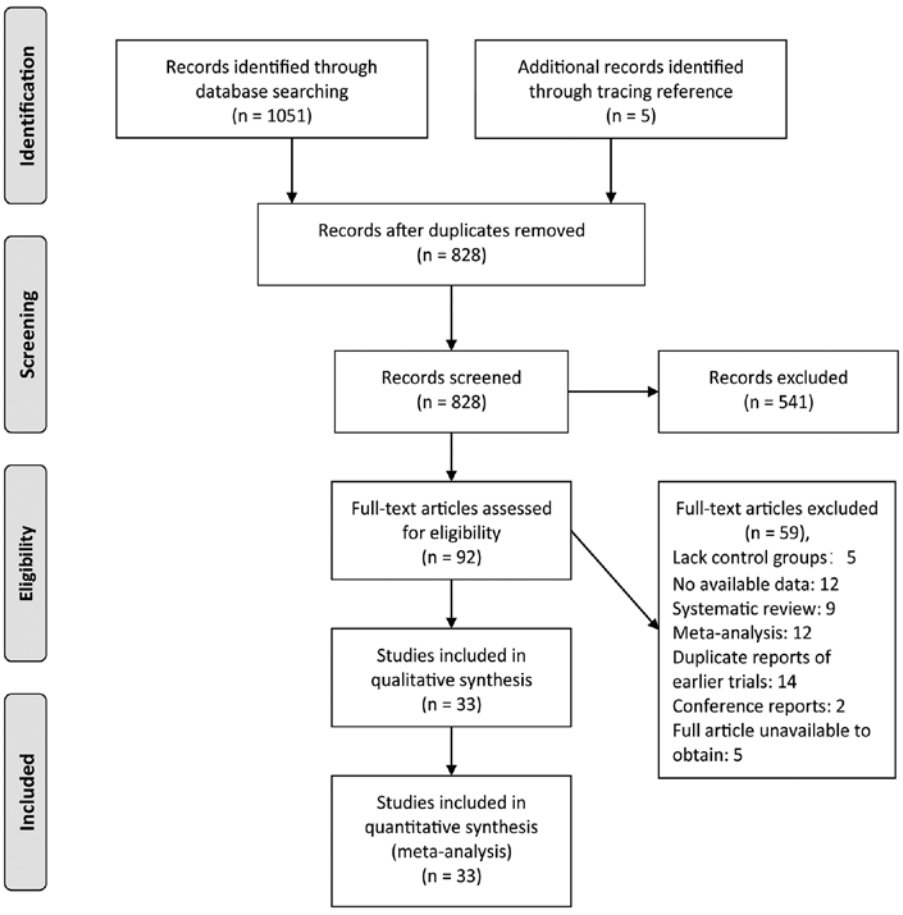

Fig. 1. *PRISMA flow diagram of search.*

Pairwise Meta-analysis for Efficacy

The traditional pairwise meta-analysis was performed to directly evaluate the efficacy of intrawound treatments for prophylaxis of SSI (Fig. 4). The outcome indicator was the SSI rate. Overall, the combined results showed a significantly lower SSI rate on the group of intrawound treatments than CG (OR = 0.41; 95% CI, 0.31-0.55). For subgroups, the results indicated that the groups of VA (OR = 0.52; 95% CI, 0.38-0.71), PI (OR = 0.09; 95% CI, 0.04-0.22), VA+PI (OR = 0.34; 95% CI, 0.14-0.82), and GM (OR = 0.16; 95% CI, 0.04-0.71) were associated with

Table 1. *The characteristics of the included studies.*

Study Year	Country	Design	Type of Operation	Sample Size (T vs C)	Mean Age (T vs C, year)	Gender (M/F)	Follow-up (month)	Nature of SSI	Type of T	Infection Rate	
										T	C
Gaviola 2016 (30)	USA	RCS	Instrumented spinal fusion	116 vs 210	62 vs 55	184/142	≥ 3	Deep + Superficial	VA	6/116	23/210
Sombat 2019 (31)	Thailand	RCS	Instrumental spinal surgery	265 vs 135	52.12 vs 55.18	168/238	≥3	Deep	VA	9/265	4/135
Horii 2018 (32)	Japan	RCS	Posterior instrumented surgery	694 vs 2165	68.5 vs 65.0	1325/1529	≥12	Deep + Superficial	VA	12/1325	21/1529
Prashant 2020 (33)	Turkey	RCS	Posterior spine surgery	88 vs 70	50.77 vs 49.31	66/92	≥12	Deep	VA	3/88	1/70
Lee 2016 (34)	Korea	RCS	Posterior spine surgery	275 vs 296	50.2 vs 52.1	272/299	≥12	Deep + Superficial	VA	15/275	31/296
Tubaki 2013 (35)	India	RCT	Open spine surgery	433 vs 474	44.3 vs 46.6	509/398	≥3	Deep + Superficial	VA	7/433	8/474
Martin 2015 (36)	USA	RCS	Posterior cervical surgery	115 vs 174	62.3 vs 57.6	149/140	≥1	Deep + Superficial	VA	6/115	12/174
Mirzashahi 2018 (37)	Iran	RCT	Open spine surgery	193 vs 187	NA	135/245	≥1	Deep + Superficial	VA	10/193	5/187
Sweet 2011 (38)	USA	RCS	Instrumented spinal fusions	911 vs 821	56 vs 53	873/859	Mean 30	Deep	VA	2/911	21/821
Devin 2018 (39)	USA	RCS	Posterior spine surgery	966 vs 1090	60.5 vs 59.5	1014/1042	≥1	Deep + Superficial	VA	21/966	56/1090
Heller 2015 (40)	USA	RCS	Open spine surgery	342 vs 341	55.3 vs 49.1	323/360	≥3	Deep + Superficial	VA	4/342	13/341
Caroom 2013 (41)	USA	RCS	Posterior cervical instrumentation	40 vs 72	59.8 vs 56.4	NA	≥6	NA	VA	0/40	11/72
Hey 2017 (42)	Singapore	RCS	Open spine surgery	117 vs 272	45 vs 48	197/97	≥3	Deep + Superficial	VA	1/117	17/272
Kim 2013 (43)	Korea	RCS	Instrumented spinal fusions	34 vs 40	57.88 vs 60.05	38/36	NA	Deep + Superficial	VA	0/34	5/40
Thompson 2018 (44)	USA	RCS	Growing spine surgery	104 vs 87	NA	NA	≥3	Deep	VA	5/104	12/87
Hill 2014 (45)	USA	RCS	Posterior spine surgery	150 vs 150	54.14 vs 58.33	147/153	≥1	Deep + Superficial	VA	5/150	11/150
Li 2018 (46)	China	RCS	Posterior spine surgery	355 vs 320	53.5 vs 52.6	325/350	≥12	Deep	VA	4/355	13/320
Tian 2018 (47)	China	RCS	Open spine surgery	297 vs 267	60.1 vs 57.5	324/240	≥12	NA	VA	7/297	15/267
Garg 2018 (48)	USA	RCS	Growing spine surgery	228 vs 310	13.8 vs 14	149/389	≥3	Deep	VA	7/221	6/304
Vincenzo 2017 (17)	Italy	RCT	Instrumented spinal surgery	25 vs 25	41.4 vs 42.1	20/30	≥1	Deep + Superficial	PI	0/25	3/25

Abbreviations: RCS, retrospective cohort studies; RCT, randomized controlled trial; T: treatment group; C, control group; VA, vanconycin; PI, povidone-iodine; VA+PI, vanconycin+povidone-iodine; HP, hydrogen peroxide; PI+HP, povidone-iodine+hydrogen peroxide; GM, gentamicin; NA, not available.

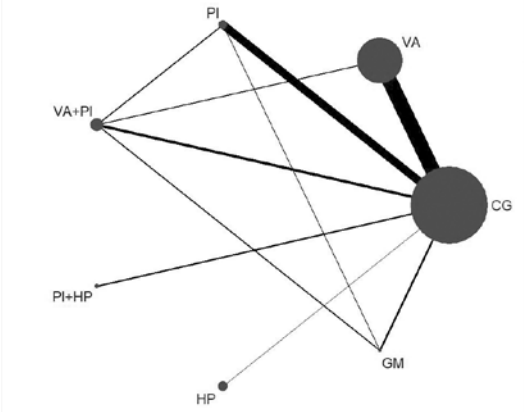

Fig. 2. *The Network Evidence Plot of Treated Comparisons.*
Treatment comparisons for control group (CG), vancomycin (VA), povidone-iodine (PI), hydrogen peroxide (HP), gentamicin (GM), vancomycin + povidone-iodine (VA+PI), and povidone-iodine + hydrogen peroxide (PI+HP) are presented in network plots. The size of a circle represents the number of studies of the specific treatment. Connecting lines represents direct comparisons of interventions while thicker lines indicates more connecting studies.

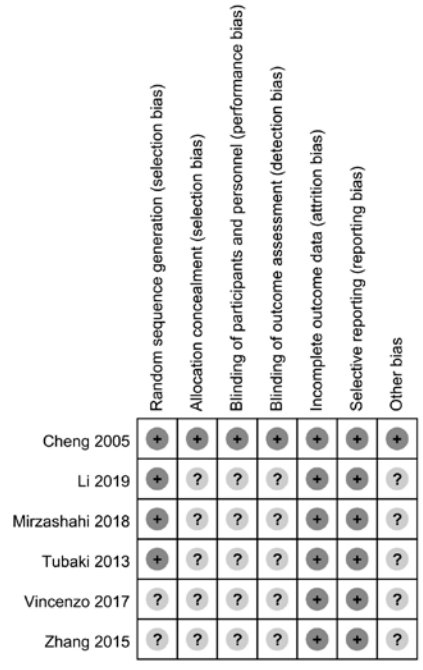

Fig. 3. *Risk of Bias of Randomized Controlled Studies (RCTs).*
Review authors' judgments about each risk of bias item presented across all included RCTs. (+) = Low risk; (–) = High risk; (?) = Unclear.

Table 2. *Quality Assessment of the Cohort Studies according to the NOQAS.*

Study	Selection	Comparability	Outcome	Total Score
Gaviola 2016 (30)	3	1	2	6
Sombat 2019 (31)	3	2	2	7
Horii 2018 (32)	3	1	3	7
Prashant 2020 (33)	3	1	2	6
Lee 2016 (34)	3	2	3	8
Martin 2015 (36)	3	1	2	6
Sweet 2011 (38)	3	2	2	7
Devin 2018 (39)	3	2	2	7
Heller 2015 (40)	3	1	2	6
Caroom 2013 (41)	3	2	2	7
Hey 2017 (42)	3	2	2	7
Kim 2013 (43)	3	2	2	7
Thompson 2018 (44)	3	0	3	6
Hill 2014 (45)	3	1	2	6
Li 2018 (46)	3	2	3	8
Tian 2018 (47)	3	2	3	8
Garg 2018 (48)	3	2	3	8
Luo 2015 (52)	3	1	2	6
Li 2016 (53)	3	2	2	7
Herwijnen 2016 (54)	3	2	3	8
Meza 2020 (18)	3	0	2	5
Tomov 2015 (55)	3	1	2	6
Addisu 2019 (56)	3	2	2	7
Ulivieri 2011 (19)	3	0	2	5
Chen 2020 (63)	3	2	2	7
Li 2017 (64)	3	2	2	7
Han 2016 (15)	3	2	2	7

Abbreviations: NOQAS, The Newcastle-Ottawa Quality Assessment Scale.

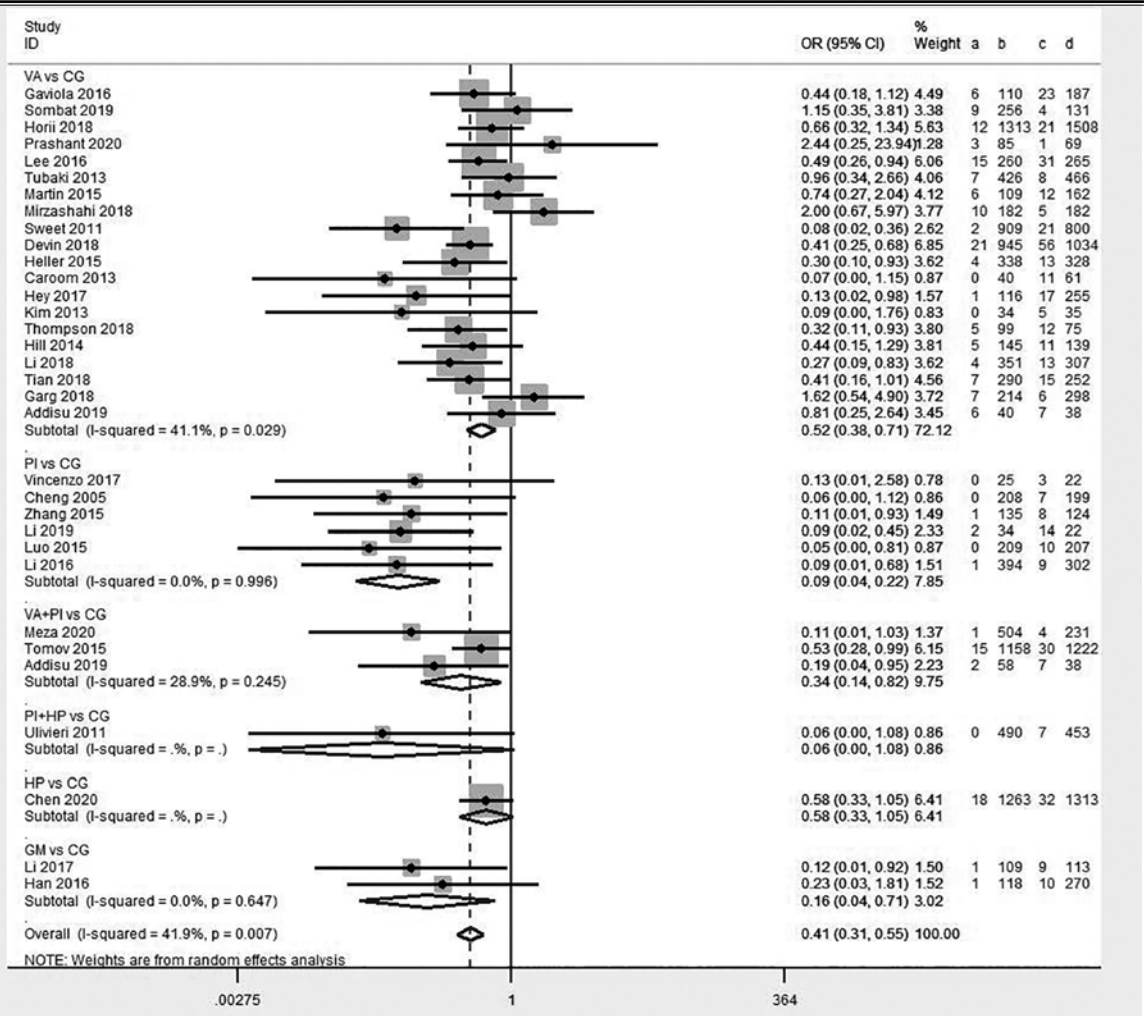

Fig. 4. *A Forest plot of pairwise meta-analysis for different intrawound treatments versus control group.*
The graph presents the overall efficacy for all intrawound treatments compared with control group (CG). VA, vancomycin; PI, povidone-iodine; VA+PI, vancomycin + povidone-iodine; HP, hydrogen peroxide; PI+HP, povidone-iodine + hydrogen peroxide; GM, gentamicin; OR, odds radio; CI, confidence interval.

a significant reduction in the SSI rate compared with CG. However, there were no significant differences between the PI+HP (OR = 0.06; 95% CI, 0.00-1.08) and HP (OR = 0.58; 95% CI, 0.33-1.05) compared with CG. For sensitivity analyses, we excluded 2 studies (18,19) with "high risk" of bias. There was no significant influence on the overall outcomes, indicating that the overall meta-analysis results were promising.

Network Meta-analysis

All available trials, including 6 treatment strategies and 1 CG were analyzed in the network meta-analysis. We detected that there was no evidence of significant global inconsistency (P = 0.23). The inconsistency plot was employed to test the inconsistency among all evidence loops (Fig. 5). Four triangular loops (CG–PI–GM loop, CG–PI–VA+PI loop, CG–VA+PI–GM loop and CG–VA–VA+PI loop) were presented in this analysis. The PI–VA+PI–GM loop was formed only by a 3-arm trial, so exploring its inconsistency was not needed. The 95% CI of IF values of 4 loops reached 0, indicating that no significant inconsistency was detected.

Based on the network comparisons, the treatments of VA (OR = 0.53; 95% CI, 0.39-0.71), PI (OR = 0.10; 95% CI, 0.04-0.23), and VA+PI (OR = 0.25; 95% CI, 0.11-0.58) were found to be significantly more effica-

cious than CG, when evaluating reduction of SSI rate. PI+HP (OR = 0.06; 95% CI, 0.00-1.20), HP (OR = 0.58; 95% CI, 0.22-1.54), and GM (OR = 0.33; 95% CI, 0.11-1.05) were found to have no significant differences compared with CG. The treatment of PI resulted in a lower SSI rate compared with VA (OR = 0.19; 95% CI, 0.08-0.45) and HP (OR = 0.17; 95% CI, 0.05-0.60). There were no significant differences for any other comparison according to the network meta-analysis results. The results of network comparisons are shown in Table 3.

Interventions were ranked in the order of their efficacy for preventing SSI based on SUCRA. Relative SUCRA values showed that PI (88.7%) ranked first in the treatment effect on reducing SSI, followed by PI+HP (84.1%), VA+PI (62.5%), GM (50.7%), VA (32.4%), and HP (30.1%); CG (3.4%) ranked last (Fig. 6).

Publication Bias

The funnel plot for assessment of publication bias was presented in Fig. 7. There was no obvious asymmetry in the funnel graph, implying less likelihood of publication bias.

Discussion

SSI remains a clinically common disease. Justin V. C. Lemans (59) performed a meta-analysis to demonstrate that intrawound treatments of VA and PI could reduce deep SSI in instrumented spinal surgery. Traditional pairwise meta-analysis methods focus on the comparison between 2 interventions. Although various intrawound treatments have been reported, the best treatment remains under debate. In this work, we aimed to determine the protective benefit of different intrawound treatments. Thirty-three clinical studies, involving 6 strategies were evaluated. According to the results of pairwise meta-analysis and network meta-analysis, VA, PI, and VA+PI showed significant benefits in the outcomes. Meanwhile, HP exhibited no better performance than CG. The results of GM differed between pairwise meta-analysis and network meta-analysis. GM was not recommended as an effective intrawound treatment compared with CG because network meta-analysis's process of combining direct and indirect evidence could increase the credibility of results. SUCRA was applied to rank involved intrawound treatments, which provided an opportunity to choose the best treatment and avoid the worst treatment. The highest SUCRA value suggested that the application of PI irrigation was the best intervention and that CG showed the worst efficacy.

Intraoperative intravenous antibiotics have been proven to be the safe and efficacious methods in

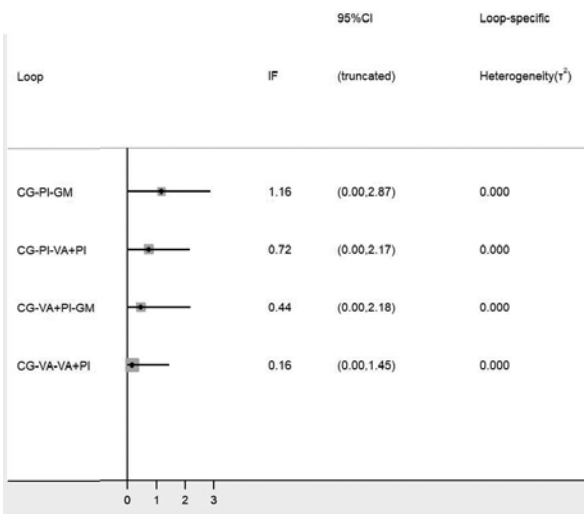

Fig. 5. *The inconsistency plot for direct and indirect comparisons.*
IF = inconsistency factor; CI = confidence interval; CG = control group; VA = vancomycin; PI = povidone-iodine; VA+PI = vancomycin + povidone-iodine; HP = hydrogen peroxide; PI+HP = povidone-iodine + hydrogen peroxide; GM = gentamicin.

Table 3. *Results of the network meta-analysis on SSI rate.*

PI						
1.58 (0.07, 34.58)	**PI+HP**					
0.38 (0.13, 1.13)	0.24 (0.01, 5.30)	**VA+PI**				
0.29 (0.09, 1.00)	0.19 (0.01, 4.47)	0.76 (0.21, 2.80)	**GM**			
0.19 (0.08, 0.45)*	0.12 (0.01, 2.32)	0.48 (0.20, 1.15)	0.63 (0.19, 2.07)	**VA**		
0.17 (0.05, 0.60)*	0.11 (0.00, 2.39)	0.43 (0.12, 1.56)	0.57 (0.13, 2.56)	0.90 (0.33, 2.48)	**HP**	
0.10 (0.04, 0.23)*	0.06 (0.00, 1.20)	0.25 (0.11, 0.58)*	0.33 (0.11, 1.05)	0.53 (0.39, 0.71)*	0.58 (0.22, 1.54)	**CG**

Abbreviations: Treatments are reported in order of ranking of efficacy for preventing surgical site infection (SSI), PI, povidone-iodine; PI+HP, povidone-iodine + hydrogen peroxide; VA+PI, vancomycin + povidone-iodine; GM, gentamicin; VA, vancomycin; HP, hyrogen peroxide; GC, control group; *represents statistical difference.

terms of reducing risk of SSI (9); however, there are several areas where intravenous antibiotics fail to reach, including hypoxic tissue, devitalized tissue, dead space, and local hematoma (60). Applications of local antibiotics represent important strategies as the adjuvant therapy to systemic perioperative antibiotics. The topical use of antibiotics could reach high doses within a short time and avoid the systemic toxicity when delivered into the surgical wound (10). It is reported that the topical use of GM could be successful in preventing SSI in spine surgery (15,58), which is inconsistent with our research. Several previous meta-analyses have demonstrated that use of VA powder in spine surgery might be effective in preventing of SSI (16,61) and these results are analogous to our findings; however, we could not ignore the risks of routine treatment. Adhikari (33) found that VA powder might have an effect on the underlying pathogens and potentially cause further increase in gram-negative infections. A systematic review assessing 16 articles summarized that the overall adverse event rate was 0.3% after using VA powder (62). The rare and potentially devastating complications, including pseudarthrosis, irreversible renal toxicity, and life-threatening anaphylaxis have been mentioned in our concerns (35).

PI, which is widely used to disinfect skin, mucous membranes, and wounds, has the ability to eradicate a wide spectrum of pathogens including methicillin-resistant staphylococcus aureus (MRSA) and avoid bacterial resistance (49). In previ-

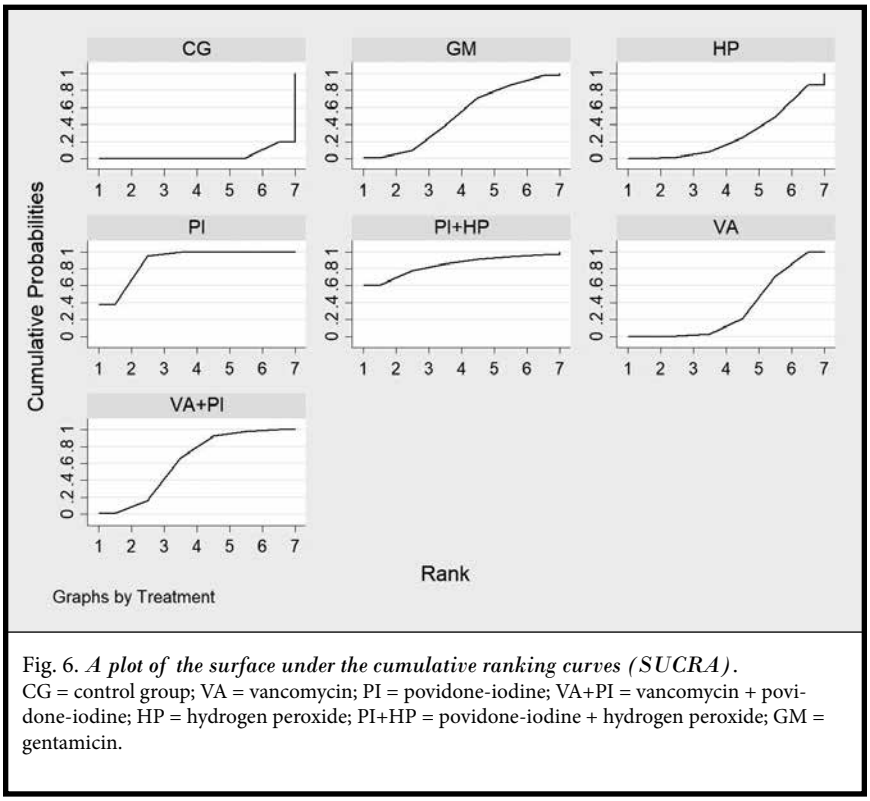

Fig. 6. *A plot of the surface under the cumulative ranking curves (SUCRA).*
CG = control group; VA = vancomycin; PI = povidone-iodine; VA+PI = vancomycin + povidone-iodine; HP = hydrogen peroxide; PI+HP = povidone-iodine + hydrogen peroxide; GM = gentamicin.

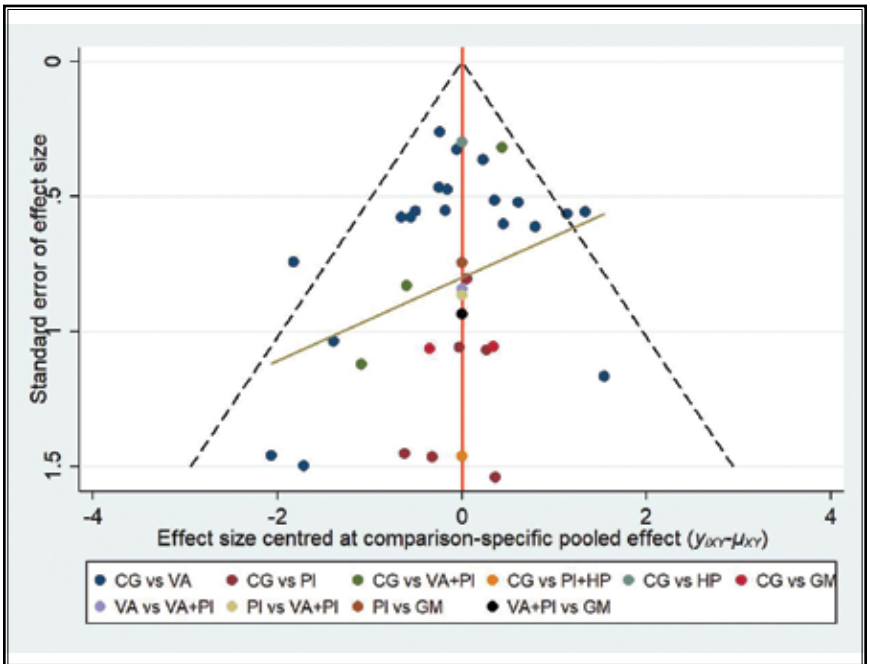

Fig. 7. *A funnel plot to confirm the risk of publications bias for included literatures.*
Points of different colors represent different interventions. CG= control group; VA = vancomycin; PI = povidone-iodine; VA+PI = vancomycin + povidone-iodine; HP = hydrogen peroxide; PI+HP = povidone-iodine + hydrogen peroxide; GM = gentamicin.

ous meta-analysis, the authors included 24 RCTs and demonstrated that the topical use of PI showed efficacy to reduce SSI rate (63). A study in vitro reported that PI with 5% or higher concentrations might cause toxicity in animal cells (64). PI diluted to 1-3% concentration possessed effective bactericidal activity with few cytotoxic effects (17,53). Cheng (49) also suggests that surgical wound was managed by adequate debridement and copious normal saline irrigation after PI irrigation. According to our study, the effect of PI on reducing SSI was much better than other intrawound treatments.

HP is a powerful oxidizing reagent that is widely used in disinfection and wound irrigation. Bannister (65) suggests that HP irrigation led to a 14% overall bleed reduction in arthroplasty surgery. Chen (57) emphasizes the efficacy of wound irrigation with HP for reducing SSI in the spine surgery. However, our results based on direct and indirect evidence showed that HP had no significant benefits in preventing SSI. Considering the potential complications of cytotoxicity and air embolism, we recommend that surgeons use this treatment with caution.

The outcome indicators of this study are superficial and deep SSI. The SSI is categorized as "superficial SSI," "deep SSI," and "organ/space SSI" following the United States Centers for Disease Control and Prevention (CDC) guidelines (66). Early diagnosis is essential for favorable outcome, involving the interpretation of clinical symptoms, laboratory values, radiological findings, and occasionally biopsy and culture (67). "Superficial SSI" is considered mild and is commonly treated with short-term antibiotic medication and local wound care (16). "Deep SSI" tends to result in an unexpected worsening clinical outcome (32) and unavoidably involves prolonged intravenous antibiotics, surgical debridement, and potentially implant removal (43).

This network meta-analysis studied the effect of intrawound treatments on the incidence of SSIs after spine surgery. The main findings of this study were that VA powder use or PI irrigation at operative closure provided significant protection against SSI. It was also worth mentioning that PI irrigation was regarded as the most effective strategy. GM and HP were not recommended due to their lack of effectiveness. There are several strengths in this study: 1) this is the first network meta-analysis representing the most comprehensive analysis on preventive strategies of intrawound treatments; 2) the comprehensive search strategy is arranged and the funnel plot shows no obvious publication bias; 3) this review included a large sample of patients; 4) the SUCRA value is adopted to rank the comparative effects of different treatments for better clinical applications; 5) we assess the inconsistency using both a global test and inconsistency factor values. The 2 major analyses demonstrate no substantial inconsistency.

Limitations

Nevertheless, some limitations deserve further discussion. Firstly, only 6 RCTs are included in this systematic review. Retrospective cohort studies tend to exaggerate the real results, although most of them are high-quality according to the NOQAS. More high-quality RCTs need to be included to obtain convincing conclusions. Secondly, the population of this study involves both adult and pediatric cohorts, patients with tumors, congenital diseases, or degenerative diseases. There is no subgroup analysis for ages and type of diseases which might have an influence on the overall pooled analysis. We defined the application of saline solution and no intrawound treatment as the CG, which might ignore their heterogeneity. The GM impregnated sponge and GM microspheres are grouped together, which may also contribute to the potential heterogeneity. Thirdly, although SUCRA has been widely used in network meta-analysis, findings of SUCRA can be misleading. The calculation of ranking probabilities mostly relies on the point estimates (OR) and ignore their CI (26). Meanwhile, SUCRA is unable to show whether the difference between treatments is clinically meaningful. Results of SUCRA should be interpreted with caution, because high values may only provide supportive rather than conclusive evidence of treatment options. In consideration of limitation of SUCRA, we only use it to determine the best available treatment. Fourthly, follow-up periods are variable and the sample size of HP is small. Finally, additional research is needed to compare the complications of different treatments and the benefits of various dosages.

Conclusions

In conclusion, we find that VA and PI show promising results on reducing SSI. PI is recommended as the most efficacious intrawound treatment to prevent SSI after spine surgery. Considering the limitations of this analysis, our results need to be validated by further research with larger sample sizes.

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