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Intrawound Treatment for Prevention of Surgical Site Infections in Instrumented Spinal Surgery: A Systematic Comparative Effectiveness Review and Meta-Analysis

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Abstract

Study Design: Systematic review and meta-analysis.

Objectives: To determine the efficacy of intrawound treatments in reducing deep surgical site infections (SSIs) in instrumented spinal surgery.

Methods: The electronic databases MEDLINE, EMBASE, and Cochrane were systematically searched for intrawound treatments for the prevention of SSIs in clean instrumented spine surgery. Both randomized controlled trials and comparative cohort studies were included. The results of included studies were pooled for meta-analysis.

Results: After full text- and reference screening, 20 articles were included. There were 2 randomized controlled trials and 18 observational studies. Sixteen studies investigated the use of intrawound antibiotics, and 4 studies investigated the use of intrawound antiseptics. The relative risk of deep SSI for any treatment was 0.26 (95% confidence interval [CI] 0.16-0.44, $P < .0001$), a significant reduction compared with controls receiving no treatment. For patients treated with local antibiotics the relative risk was 0.29 (95% CI 0.17-0.51, $P < .0001$), and patients treated with local antiseptics had a relative risk of 0.14 (95% CI 0.05-0.44, $P = .0006$).

Conclusions: Both the use of antibiotic and antiseptic intrawound prophylactics was associated with a significant 3 to 7 times reduction of deep SSIs in instrumented spine surgery. No adverse events were reported in the included studies.

Keywords

surgical site infection, postoperative infection, prophylaxis, prevention, intrawound, povidone-iodine, vancomycin

Introduction

Surgical site infections (SSIs) are serious adverse events with substantial patient morbidity and increased mortality.[1] The incidence of SSIs is highly dependent on the type of surgery; in spinal surgery, the overall incidence is around 4%.[2] The incidence is substantially higher in implant-related surgery, with SSIs developing in 9.4% of patients undergoing instrumented spinal surgery for traumatic fractures and in up to 19.2% of patients undergoing pediatric deformity surgery.[3,4] SSIs in instrumented spinal surgery are a challenge to treat.[5] Besides having a profound impact on patients, SSIs are a substantial financial burden on the health care system as well, costing up to $30 000 per patient for patients undergoing

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orthopedic surgery.[6,7] With the increasing focus on preventing complications and limiting health care costs, finding new ways to avert SSIs is of critical importance. Aseptic surgical techniques and perioperative intravenous antibiotic prophylaxis have proven to be effective.[8-11] For other measures like nasal *Staphylococcus aureus* decontamination, preoperative chlorhexidine baths, and many forms of surgical attire, the effect has not been shown unequivocally.[12-14] In the past years, there has been an increased interest in additional decontamination of the surgical wound before closure. One of the strategies involves the application of antibiotics, like vancomycin, directly into the wound.[15-17] Alternatively, antiseptic irrigation solutions are used, like povidone-iodine and hydrogen peroxide.[18] The former antiseptic is most often used, in varying concentrations.[18] Antiseptics have the advantage of not inducing bacterial resistance. They are, however, cytotoxic when used in high concentrations.[19,20] Current evidence regarding efficacy and side effects associated with the use of intrawound antibiotics and antiseptics is still limited. Therefore, their use is not generally adopted in clinical practice.

The aim of this study was to determine the efficacy and potential side effects of intrawound prophylactic treatments in instrumented spinal surgery. A secondary goal was to compare the different methods used as intrawound treatment. Since meta-epidemiological research has shown that for surgical research questions, both randomized controlled trials (RCTs) and well-designed observational comparative study designs should be analyzed,[21-24] we included both to make this review as representative and comprehensive as possible.

Methods

This systematic review and meta-analysis was performed in accordance with the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25] and the Cochrane Handbook for Systematic Reviews of Interventions.[26] The electronic databases MEDLINE, EMBASE, and Cochrane were systematically searched for articles that investigated the use of intrawound treatments for the prevention of SSIs in all types of clean instrumented spinal surgery. We searched for all possible types of prophylactic wound treatment and all phrases that were synonymous with SSI. The complete syntax used for each database can be found in the appendix.

Eligibility Criteria and Study Selection

Studies were limited to articles published in English, German, or French until April 16, 2018, with no restriction on publication date. Articles were screened for eligibility by 2 independent reviewers (JVCL and WB). Any disagreement between the reviewers was resolved through discussion or, if no consensus was reached, through consultation of a third reviewer (MCK). Reference screening and citation tracking was performed to find additional relevant articles. Human, comparative studies that investigated clean, instrumented spinal surgery were included. Treatment had to be given peroperatively, inside the wound before closure, with the intention to prevent infection. Studies with a reported mean follow-up time of less than 3 months, studies from which deep SSI rates in instrumented patients could not be extracted, studies with treatments that were applied onto the implants instead of into the wound, and studies with treatments in which a prolonged effect was intended (eg, antibiotic bone cement) were excluded. To minimize the apparent risk of bias as a result of selection by indication (treatment allocation based on surgeons judgment), these studies were also excluded.[27]

Data Collection and Study Quality Evaluation

Relevant study data was collected by one reviewer (JVCL) and checked by a second reviewer (SPJW). Disagreements were resolved through discussion. Deep SSI rates in instrumented patients were extracted from the article or were calculated by using the information reported in the article. We assessed the presence and extent of heterogeneity between studies based on data extracted from each article. Study quality for observational studies and randomized trials was determined using the Methodological Index for Non-Randomized Studies (MINORS) grading tool.[28] The articles were independently graded by 2 reviewers (JVCL and SPJW).

Statistical Analysis

We combined the studies in a random-effects meta-analysis to calculate the relative risk and the 95% confidence intervals (CIs) by using the restricted maximum likelihood estimator.[29] Due to the expected few cases in either group, a relative outcome measure was chosen in order to better illustrate differences. The Mantel-Haenszel method with a fixed-effects model was used to provide an unbiased pooled estimate. To gauge the effect of heterogeneity (ie, the different clinical settings and study methodologies), Tau^2 was used as an estimate of the total amount of statistical heterogeneity. The I^2 index was used to quantify the influence of heterogeneity on the final result. Heterogeneity was considered relevant when I^2 was >50%. Publication bias, based on standard error, was explored with a funnel plot with random-effects pseudo–confidence limits.

To assess the effect of the different intrawound prophylactic methods, a subgroup analysis of both antibiotics and antiseptics was done. Furthermore, to assess the effect of study quality, a sensitivity analysis was done based on study quality. We arbitrarily divided the included studies in 3 groups, based on their MINORS score. Low-quality studies were defined as a MINORS score $\leq$12 (out of a maximum of 24). Medium-quality studies were defined as a MINORS score between 12 and 16, and high-quality studies were defined as a score $\geq$16.

Since the effect of prophylactic treatment was compared with historical control groups in many of the retrospective studies, the bias of a potential time-related effect caused by improved infection prevention over time was studied with a weighted regression analysis, by plotting the incidence of SSIs

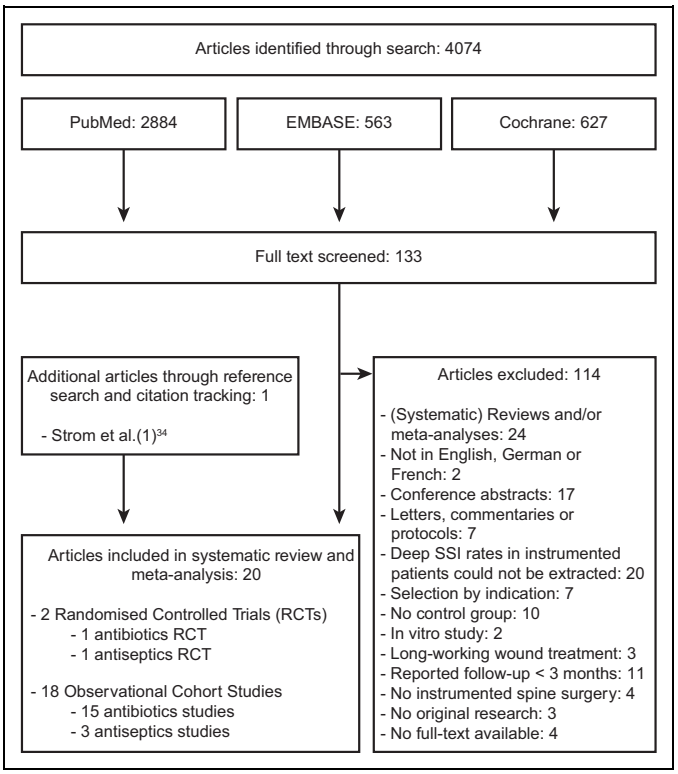

Figure 1. PRISMA flow diagram.
RCT, randomized controlled trial; SSI, surgical site infection.

in the control groups against the year of operation. The Metafor package (R Foundation for Statistical Computing, Vienna, Austria, 2012) was used for all statistical analyses. A $P < .05$ was considered to be significant.

Results

Search

The search in the MEDLINE, EMBASE, and Cochrane libraries yielded a total of 4074 results. After removal of duplicates and title and abstract screening, 133 articles were eligible for full-text assessment. After review, 114 articles were excluded. Through reference screening and citation tracking, one additional article was found that matched the eligibility criteria. Finally, a total of 20 studies were included in the systematic review and meta-analysis. A PRISMA flowchart of this process can be found in Figure 1.

Baseline Characteristics

Of the 20 included studies, 2 were RCTs[30,31] and 18 were observational cohort studies (Table 1).[32-49] Eight studies investigated many different types of spinal surgery.[30,38-41,43,46,47] Five studies investigated deformity surgery, in either adults,[42] children,[45,48,49] or both.[32] One study investigated all types of spinal surgery in children.[44] Three studies investigated cervical spinal surgery,[34,36,37] and 3 studies investigated thoracolumbar or lumbar spinal surgery.[31,33,35] Sixteen studies investigated the use of intrawound antibiotics (all studies investigated vancomycin),[30,33-42,44-48] while 4 studies investigated the use of intrawound irrigation with antiseptics (all studies investigated povidone-iodine, one study also added hydrogen peroxide).[31,32,43,49] Baseline equivalence regarding characteristics between control and intervention groups was present in 11 studies[30-35,37-39,47,49] and unclear or not present in 9 studies.[36,40-46,48] Characteristics of the intervention treatments and the use of perioperative antibiotic prophylaxis can be found in Table 2.

Fourteen studies provided a clear definition of SSI. In 5 studies,[32,44-46,48] this was the (deep) SSI definition used by the Centers for Disease Control and Prevention.[50] Three studies defined SSI as a combination of clinical symptoms, elevated serum inflammation markers (erythrocyte sedimentation rate, C-reactive protein, white blood cell count), and bacterial culture results.[31,33,43] One study solely relied on the results of culture and/or radiographic findings.[39] Five studies used the need for reoperation or nonresponse to antibiotics,[36,38,42,47,49] and 6 studies did not provide a clear SSI definition.[30,34,35,37,40,41]

Study Quality and Heterogeneity

The median MINORS quality score for all studies was 14 (range 11-17) out of a maximum score of 24. The 2 RCTs included in this review yielded a higher median score of 16.5 (range 16-17), while the observational studies had a median score of 13.5 (range 11-17). Some statistical heterogeneity was observed when looking at the pooled result with a Tau^2 of 0.43. The I^2 index for heterogeneity remained <50% ($I^2 = 38.6\%$) and may represent moderate heterogeneity.

Meta-Analysis

Deep SSIs were reported in 38 of the 3439 patients that received intrawound treatments (1.1%), compared with 189 deep SSIs in the 4529 control patients (4.2%). Table 3 contains the deep SSI rates for all studies. With this data, a meta-analysis was performed (Figure 2). When the results of the antibiotic interventions and the antiseptic irrigation interventions were pooled, the relative risk for deep SSI was 0.26 (95% CI 0.16-0.44, $P < .0001$). For the patients treated with local antibiotics, the pooled relative risk for deep SSI was 0.29 (95% CI 0.17-0.51, $P < .0001$) when compared with the control group. Patients that were irrigated with antiseptics had a pooled relative risk of 0.14 (95% CI 0.05-0.44, $P = .0006$). If heterogeneity would be ignored, the Mantel-Haenszel method that uses the fixed-effects model yields even lower relative risks with a relative risk of deep SSI for antibiotics and antiseptics combined of 0.23 (95% CI 0.16-0.33), a relative risk for antibiotics of 0.26 (95% CI 0.18-0.37), and a relative risk for antiseptics of 0.05 (95% CI 0.01-0.31).

Pooling the high-quality studies (5 studies) resulted in a relative risk of 0.33 (95% CI 0.08-1.42). Pooling the medium (9 studies) and lower (6 studies) quality studies resulted in a

Table 1. Study Demographics.

Author	Year	Study Type	Intervention	Contemporary Study Populations	Type of Surgery	MINORS Score	Follow-up Length	Adverse Events
Intrawound antibiotics								
Garg et al	2018	Retrospective cohort	Vancomycin	Historical controls	Pediatric posterior spinal fusion	16	Minimum: 3 months; intervention: median 17 months; control: median 26 months	None
Thompson et al	2018	Retrospective cohort	Vancomycin	Historical controls	Pediatric scoliosis growing rod surgery	13	Minimum: 3 months	None
Haller et al	2017	Retrospective cohort	Vancomycin	Historical controls	Rib-based distraction surgeries	14	Minimum: 6 months	None
Hey et al	2017	Retrospective cohort	Vancomycin	Contemporary groups	General instrumented spinal surgery	15	Minimum: 3 months	None
Liu et al	2015	Retrospective cohort	Vancomycin	Historical controls	Adult instrumented spinal surgery	14	Minimum: 3 months	None
Hill et al	2014	Retrospective cohort	Vancomycin	Contemporary groups	General spinal surgery	14	Intervention: mean 8.76 months; control: mean 10.03 months	None
Emohare et al	2014	Retrospective cohort	Vancomycin	Contemporary groups	General spinal surgery	12	Intervention: mean 20.7 months; control: mean 21.7 months	NR
Theologis et al	2014	Retrospective cohort	Vancomycin	Historical controls	Complex adult deformity reconstruction	11	Intervention: mean 18 months; control: mean 34 months	None
Tubaki et al	2013	RCT	Vancomycin	Contemporary groups	General spinal surgery	16	Minimum: 3 months	None
Strom et al (1)[34]	2013	Retrospective cohort	Vancomycin	Historical controls	Instrumented posterior cervical fusion	12	Minimum: 1 year	None
Strom et al (2)[35]	2013	Retrospective cohort	Vancomycin	Historical controls	Lumbar laminectomy and fusion	12	Intervention: mean 1.9 years; control: mean 4.5 years	None
Pahys et al	2013	Retrospective cohort	Vancomycin	Historical controls	Posterior cervical spinal surgery	13	Minimum: 3 months	None
Caroom et al	2013	Retrospective cohort	Vancomycin	Historical controls	Posterior cervical decompression and fusion	16	Intervention: minimum 6 months; control: mean 18 months	None
Heller et al	2013	Retrospective cohort	Vancomycin	Historical controls	General instrumented spinal surgery	14	Minimum: 3 months	None
Kim et al	2013	Retrospective cohort	Vancomycin	Contemporary groups	General instrumented spinal surgery	12	Minimum: 3 months; mean: 5.8 months	None
Sweet et al	2011	Retrospective cohort	Vancomycin	Historical controls	Instrumented thoracolumbar fusion	17	Intervention: mean 2 years; control: mean 3.4 years	None
Intrawound antiseptics								
De Luna et al	2017	Prospective cohort	Povidone-iodine	Contemporary groups	Adult and pediatric scoliosis surgery	15	Minimum: 2 years	NR
Herwijnen et al	2016	Retrospective cohort	Povidone-iodine	Historical controls	Pediatric idiopathic scoliosis surgery	13	Minimum: 8 months	None
Ulivieri et al	2011	Retrospective cohort	Povidone-iodine and H_2O_2	Historical controls	General instrumented spinal surgery	11	NR	None
Chang et al	2006	RCT	Povidone-iodine	Contemporary groups	Instrumented lumbosacral posterolateral fusion	17	Intervention: mean 19.4 months; control: mean 19.1 months	None

Abbreviations: MINORS, Methodological Index for Non-Randomized Studies; RCT, randomized controlled trial; NR, not reported; H_2O_2, hydrogen peroxide.

Table 2. Treatment Characteristics.

Author	Year	Preoperative Prophylaxis	Intraoperative Intervention Treatment	Intraoperative Control Treatment	Postoperative Prophylaxis
Intrawound antibiotics					
Garg et al	2018	IV cefazolin or vancomycin (depending on MRSA risk)	0.5-2 g of vancomycin combined with autograft and placed subfascially	NR	Standard perioperative antibiotics
Thompson et al	2018	IV cefazolin or vancomycin (depending on MRSA risk)	0.5-1 g of vancomycin powder applied over implants and bone graft before closure	NR	Oral cephalexin or oral sulfamethoxazole/trimethoprim for 2 days
Haller et al	2017	50 mg/kg IV cefuroxime	0.5 g of vancomycin powder placed between fascia and subcutaneous tissue before closure	Saline irrigation	NR
Hey et al	2017	1000 mg IV cefazolin	1 g of vancomycin powder in subfascial space	NR	IV cefazolin for 2 days
Liu et al	2015	IV cefazolin or clindamycin	0.5-2 g of vancomycin powder evenly spread over muscle, fascia, implants, and autograft before closure	1-2 L saline irrigation before wound closure	IV cefazolin or clindamycin every 8 hours for 1 day
Hill et al	2014	1000-2000 mg IV cefazolin	1-2 g of vancomycin powder into the wound before closure	NR	IV cefazolin for 1 day
Emohare et al	2014	Perioperative IV cefazolin	1 g of vancomycin powder into all wound layers prior to closure	NR	Perioperative IV cefazolin
Theologis et al	2014	Routine perioperative antibiotics	2 g of vancomycin powder in subfascial space	NR	Routine perioperative antibiotics
Tubaki et al	2013	750 mg IV cefuroxime	1 g of vancomycin powder placed directly onto the tissues, taking care not to expose bone graft or dura	1 L saline irrigation	750 mg IV cefuroxime every 8 hours for 1 day or until drain removal depending on noninstrumented or instrumented surgery
Strom et al (1)[34]	2013	IV cefazolin	1 g of vancomycin powder placed onto all tissues, taking care not to expose bone graft or instrumentation	3 L pulse lavage with bacitracin prior to bone graft placement	NR
Strom et al (2)[35]	2013	IV cefazolin	1 g of vancomycin powder placed onto all tissues, taking care not to expose bone graft or instrumentation	3 L pulse lavage with bacitracin prior to bone graft placement	NR
Pahys et al	2013	Standard IV perioperative cephalosporins	Preoperative alcohol foam disinfectant, 0.5 g of vancomycin powder added to the wound at the end of the procedure + second drain placement	NR	Standard IV perioperative cephalosporins
Caroom et al	2013	IV antibiotics according to policy	1 g of vancomycin powder applied subfascially along bone graft and instrumentation after saline irrigation	NR	IV antibiotics according to policy, continued until 24 hours after drain removal
Heller et al	2013	20 mg/kg IV cefazolin	0.5-2 g of vancomycin powder into the wound before closure	NR	1000 mg IV cefazolin every 8 hours for 1 day
Kim et al	2013	1000 mg IV cefazolin	1 g of vancomycin powder placed directly onto the tissues, taking care not to expose bone graft or dura	NR	1000 mg IV cefazolin every 8 hours for 1 day
Sweet et al	2011	2000 mg IV cefazolin	1 g of vancomycin powder sprinkled into the deep and superficial portion of the wound before closure, 1 g mixed with bone graft	NR	IV cefazolin for 1 day

(continued)

Table 2. (continued)

Author	Year	Preoperative Prophylaxis	Intraoperative Intervention Treatment	Intraoperative Control Treatment	Postoperative Prophylaxis
Intrawound antiseptics					
De Luna et al	2017	1000 mg IV cefazolin	2 L 3% povidone-iodine for 5-10 minutes, followed by 1 L saline irrigation prior to bone graft placement	2 L saline irrigation for 5-10 minutes prior to bone graft placement	1000 mg IV cefazolin every 12 hours for 2 days
Herwijnen et al	2015	Weight dependent IV flucloxacillin and gentamicin	3 L saline irrigation followed by 1 L 1% povidone-iodine for 3 minutes followed by 3 L saline irrigation	6 L saline irrigation followed by 1 L saline irrigation with 80 mg dissolved gentamicin	IV flucloxacillin every 8 hours for 1 day
Ulivieri et al	2011	2000 mg IV amoxicillin + 400 mg IV clavulanic acid	Irrigation with solution of 10 mL 10% povidone-iodine + 5 mL H_2O + 1 mL H_2O_2 for 1 minute followed by copious saline irrigation	NR	6 hours postoperative 2000 mg IV amoxicillin + 400 mg IV clavulanic acid; 1000 mg amoxicillin + 200 mg clavulanic acid for 7 days if hardware was implanted
Chang et al	2006	1000 mg IV cefazolin and 60 mg IV gentamicin	0.35% povidone-iodine irrigation for 3 minutes followed by 2 L saline irrigation	2 L saline irrigation	1000 mg IV cefazolin every 6 hours and 60 mg IV gentamicin every 12 hours for 2 days; after that, oral cefazolin for 3 days

Abbreviations: IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; H_2O_2, hydrogen peroxide.

relative risk of 0.29 (95% CI 0.18-0.49) and 0.18 (95% CI 0.08-0.40), respectively, indicating that the lower quality studies may overestimate an effect.

The regression analysis of the incidence of SSIs over time shows that the risk of deep SSI in the control groups did not decrease but rather showed a nonsignificant, inclining slope (Figure 3). From this, we can conclude that in a period of about 12 years, the incidence of deep SSI has not significantly decreased in the study populations.

To analyze publication bias, a funnel plot was made that indicated asymmetry (Figure 4). This may be explained by the difficulty to publish studies without an effect (publication bias). However, since the standard error (the *y*-axis) of the relative risks is mathematically linked to the relative risk itself, studies with few events automatically have a high standard error, which causes the clustering in the lower left corner.

Adverse Events

None of the included articles reported any adverse events such as renal toxicity, hypotension, or prolonged wound leakage. Two articles studied the potential effects of vancomycin on compromised bone healing in terms of nonunion rate.[33,34] Strom et al[34] found a nonunion rate of 5.1% for the treated group versus 5.4% for the control group ($P = 1.000$). Sweet et al[33] found no significant difference between the intervention and control groups either (0.33% for the treated group vs 0.49% for the control group). For the application of antiseptics, only Chang et al[31] investigated the nonunion rates and found no significant difference between treated patients and controls when using a 3-minute 0.35% povidone-iodine irrigation (10.8% vs 12.1%, $P = .28$).

Discussion

This systematic review and meta-analysis indicates a positive effect of perioperative intrawound prophylaxis to reduce the risk of SSI, with a relative risk of 0.26 (95% CI 0.16-0.44) compared with no intrawound treatment. When viewed separately, both antibiotics and antiseptics were significantly effective with relative risks of 0.29 ($\sim$3 times lower risk) and 0.14 ($\sim$7 times lower risk), respectively.

In the present review, we deliberately decided to include both RCTs and observational studies. The reason for this is that the RCT is no longer regarded as the only optimal design for surgical (intervention) studies, mainly due to inherent disadvantages.[22-24,51] For example, double blinding is difficult or impossible.[52] Furthermore, surgical RCTs often have very low recruitment rates, which make them less representative of usual practice.[22,53] Due to the limited financial resources, sample size is often small and the follow-up period is short, which makes these studies less useful for complication research.[22,24,51,54,55] Observational comparative studies are by design more subjected to confounders and bias. However, a large part of confounding bias in observational comparative studies can be mitigated by sound methodological practices. In fact, meta-epidemiological studies have shown that both designs provide a comparable level of evidence for surgical research questions.[21,23,55-57] To limit bias by selection on indication, we specifically addressed this item in the study selection process.

Interestingly, the only RCT investigating intrawound antibiotics found no effect of treatment.[30] However, this study investigated treatment in both instrumented and uninstrumented spine surgeries and therefore yielded a relatively low total

Table 3. Instrumented Deep Surgical Site Infection Rates.

Author	Year	Instrumented Intervention Patients	Instrumented Control Patients	Deep SSI rate in Instrumented Intervention Patients	Deep SSI Rate in Instrumented Control Patients
Intrawound antibiotics					
Garg et al	2018	228	310	3.1% (7/228)	1.9% (6/310)
Thompson et al	2018	104	87	4.8% (5/104)	13.8% (12/87)
Haller et al	2017	169	1028	1.8% (3/169)	3.5% (36/1028)
Hey et al	2017	117	272	0.9% (1/117)	3.7% (10/272)
Liu et al	2015	180	154	2.8% (5/180)	7.1% (11/154)
Hill et al	2014	128	81	0% (0/128)	7.4% (6/81)
Emohare et al	2014	78	122	0% (0/78)	3.3% (4/122)
Theologis et al	2014	151	64	2.7% (4/151)	10.9% (7/64)
Tubaki et al	2013	302	304	2.0% (6/302)	1.6% (5/304)
Strom et al (1)[34]	2013	79	92	2.5% (2/79)	10.9% (10/92)
Strom et al (2)[35]	2013	88	77	0% (0/88)	11.7% (9/77)
Pahys et al	2013	172	405	0% (0/172)	1.7% (7/405)
Caroom et al	2013	40	72	0% (0/40)	15.3% (11/72)
Heller et al	2013	342	341	0% (0/342)	3.5% (12/341)
Kim et al	2013	34	40	0% (0/34)	7.5% (3/40)
Sweet et al	2011	911	821	0.2% (2/911)	2.6% (21/821)
Intrawound antiseptics					
De Luna et al	2017	25	25	0% (0/25)	12.0% (3/25)
Herwijnen et al	2016	71	15	4.2% (3/71)	20.0% (3/15)
Ulivieri et al	2011	100	95	0% (0/100)	7.4% (7/95)
Chang et al	2006	120	124	0% (0/120)	4.8% (6/124)

Abbreviation: SSI, surgical site infection.

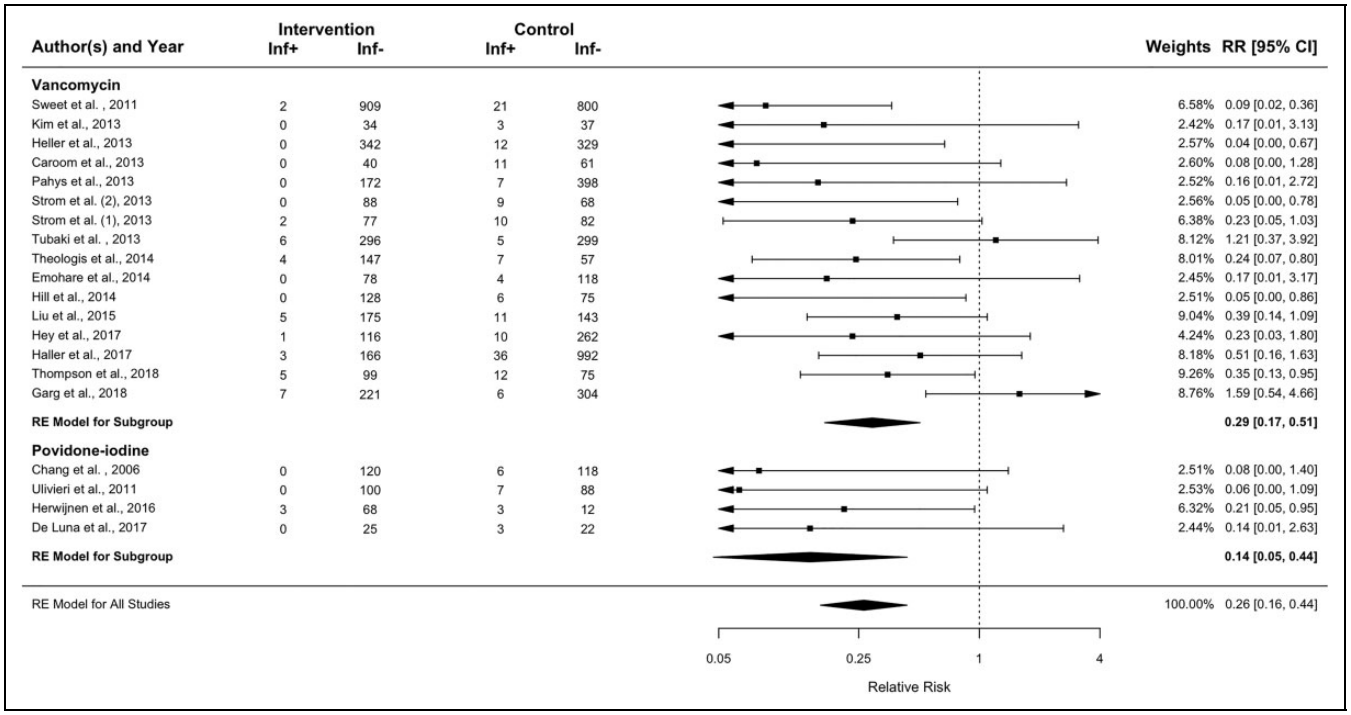

Figure 2. Forest plot of random effects model showing the relative risks and 95% confidence intervals of intrawound treatment compared to controls. A relative risk below 1 favors intervention treatment over control treatment.
RE, random effects; Inf+, number of patients with deep surgical site infection; Inf−, number of patients without deep surgical site infection; RR, relative risk; CI, confidence interval.

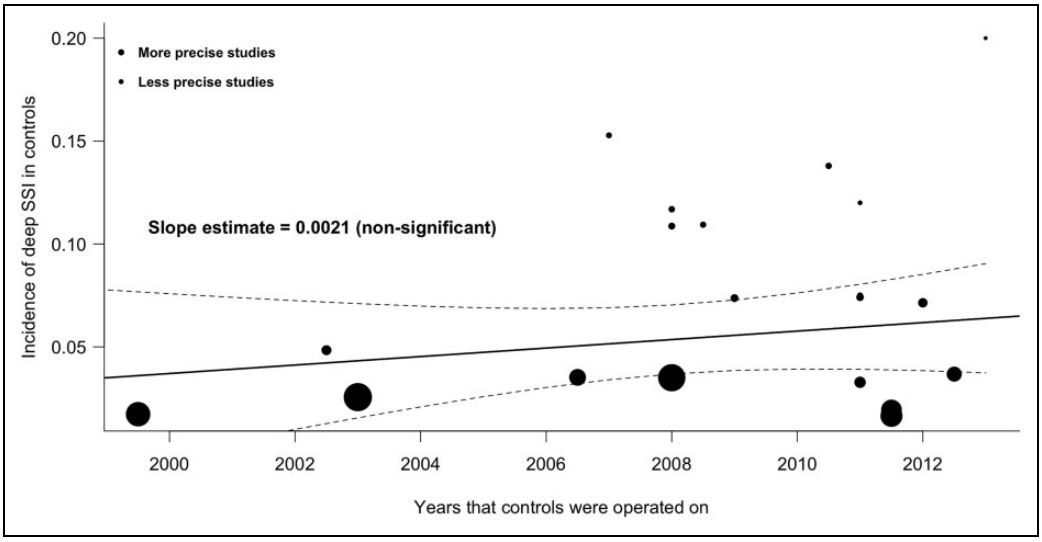

Figure 3. Weighted regression analysis of the incidence of SSI in control groups over time. Area between dashed lines is 95% confidence interval.
SSI, surgical site infection.

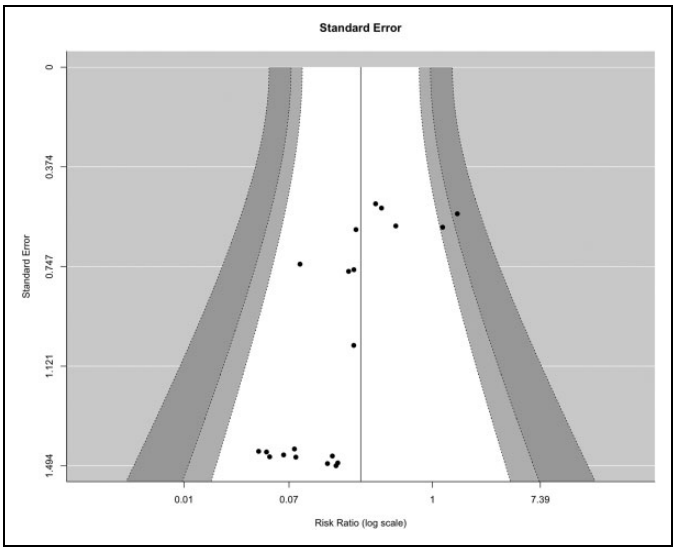

Figure 4. Funnel plot to assess publication bias. White area is within 95% pseudo–confidence interval limits.

SSI rate of 1.65%. The RCT investigating intrawound antiseptic prophylaxis in instrumented spine surgery found a reduction of deep SSIs, with a rate of 0% in the intervention group versus 4.84% in the control group.[31]

To our knowledge, this is the first systematic review and meta-analysis in spinal surgery patients to pool data from both antibiotic and antiseptic intrawound treatments into a single meta-analysis. By focusing on deep SSIs (as opposed to superficial SSIs) and instrumented patients only, we also investigated the most clinically relevant complication in a vulnerable patient group, as deep SSIs in instrumented spine surgery patients often have disastrous consequences. We are also the first to analyze SSI rates against time in a meta-regression analysis. In a recent systematic review and meta-analysis of the prophylactic use of vancomycin powder in spine surgery, Evaniew et al[17] found results similar to our study (OR 0.19, 95% CI 0.08-0.47), but they included only 8 studies, included all types of patients (implanted and non-implanted) and both deep and superficial SSIs. Also, Bakhsheshian et al[58] found an effect of vancomycin powder in the prevention of deep SSIs in their meta-analysis of 12 studies with an odds ratio of 0.23 (95% CI 0.11-0.50). With respect to intrawound povidone-iodine treatment, the meta-analysis by Mueller et al[18] that included many different types of surgery and both contaminated and infected wounds also indicated a protective effect (OR 0.70, 95% CI 0.51-0.97).

Complications and Adverse Events

Based on the literature search that we performed, few adverse events have been reported of any intrawound prophylaxis. Vancomycin is most often used as intrawound antibiotic prophylaxis because of its potency to treat infections with gram-positive skin commensals such as *Staphylococcus aureus* and *Staphylococcus epidermidis*. Side effects mentioned in the literature are sudden hypotension, renal toxicity, ototoxicity, and the Red Man syndrome,[59] which, however, have only been reported in cases when vancomycin was administered intravenously.[59] The literature on adverse events when using intrawound vancomycin mostly consists of case reports, which mention one anaphylactic reaction with circulatory collapse 30 minutes after administration,[60] one patient with unexplained renal failure and 2 patients with transient hearing loss.[61] A recent systematic review of DeFrancesco et al found only one case of adverse drug reaction (transient rash) in almost 1400 children undergoing posterior spinal surgery for early onset scoliosis, a rate of only 0.072%.[62] In addition, patients in this study that had previously shown adverse drug reactions to

intravenous vancomycin did not react to intrawound vancomycin powder. Nonunion of bone is another potential complication of local antibiotics at high concentrations. Edin et al[63] reported cytotoxicity occurring at vancomycin levels ≥10 000 μg/mL; Rathbone et al[64] found that concentrations ≥5000 μg/mL impaired the number of osteoblasts and their function; and a recent study by Eder et al[65] reported similar dose-dependent effects at concentrations of only 3000 μg/mL. The included clinical studies did not report increased nonunion rates. This is likely because the vancomycin levels in the drain fluid never exceeded 1500 μg/mL[33,65,66] and resorption into the blood was negligible, with mean serum levels not exceeding 2.5 μg/mL, far below the toxic serum concentrations.[33,66] It is important to note that vancomycin seems to be the least cytotoxic of studied antibiotics. Other antibiotics (eg, gentamicin) can be more harmful to osteoblasts and especially to cartilage when applied intra-articularly.[64] A serious disadvantage of intrawound antibiotics is its effect on antimicrobial resistance. Studying this phenomenon following intrawound use is difficult, but some studies that investigated culture findings after vancomycin use exist. One such study found no increase in the number of SSIs with vancomycin-resistant strains in patients treated with intrawound vancomycin.[67] It did, however, find significantly more infections with gram-negative bacteria. In contrast to this, however, another study found no differences in culture profiles when comparing the period before and after intrawound vancomycin.[68] Although these 2 studies have not yet shown the onset of vancomycin-resistant infections, the theoretical effects are definitely a cause for concern and therefore a preference for irrigation with antiseptics to antibiotics could be argued.

Most antiseptics are cytotoxic well before they achieve the minimal bactericidal concentration.[19] Povidone-iodine is an exception to this by achieving bactericidal concentrations before cytotoxicity occurs at the relatively low concentration of 1.3 g/L.[19] Although the included studies used substantially higher concentrations, no adverse events associated with the use of povidone-iodine were reported. Also, nonunion rates between treated patients and controls did not differ.[31]

Limitations

Our study had several limitations. First, deep SSI rates in many different types of instrumented spinal surgery were studied. This makes general applicability of the observed results difficult. Second, a publication bias based on the included studies cannot be excluded. Third, many different patient demographics and highly divergent follow-up times were present in the included studies, which caused study heterogeneity. Fourth, the SSI definitions were not similar in the included studies and were not always clearly defined, making it easier for the investigators to be biased when defining whether someone developed an SSI based on the desired outcome (expectancy bias). Finally, the amount, concentration, and method of application varied across studies, as did the type, amount, and length of the perioperative antibiotics that were used.

Conclusion

Based on data from 20 studies, we found a 3 to 7 times reduction in deep SSIs in instrumented spinal surgery when antibiotic intrawound prophylaxis (relative risk 0.29, 95% CI 0.17-0.51, $P < .0001$) or antiseptic intrawound prophylaxis (relative risk 0.14, 95% CI 0.05-0.44, $P = .0006$) was used. No adverse events were reported. Although the nonstandardized methods and the large heterogeneity of the currently investigated interventions preclude recommendation for a specific treatment regime, the application of intrawound treatments in general should be considered for instrumented spinal surgery patients.

Appendix

Search Strategy

Date of search: April 16, 2018.

Database	Search Syntax	Results
PubMed library	("Surgical Wound Infection"[Mesh] OR surgical wound infection*[tiab] OR surgical site infection* [tiab] OR SSI[tiab] OR joint infection[tiab] OR deep infection[tiab] OR postoperative wound infect*[tiab]) AND (local administration[tiab] OR local application[tiab] OR intrawound[tiab] OR intra-wound[tiab] OR intrasite[tiab] OR intra-site[tiab] OR powder[tiab] OR vancomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] OR dermacyn[tiab] OR iodine[tiab] OR povidone-iodine[tiab] OR PVP-I[tiab] OR betadine[tiab] OR chlorhexidin*[tiab] OR bacitracin[tiab] OR benzalkonium[tiab] OR castile soap[tiab] OR anti-infect*[tiab] OR antiseptic*[tiab] OR surfactant*[tiab] OR microbicides[tiab])	2884
EMBASE library	('surgical wound infection':ab,ti OR 'surgical site infection':ab,ti OR SSI:ab,ti OR 'joint infection':ab,ti OR 'deep infection':ab,ti OR 'postoperative wound infection':ab,ti) AND ('local administration':ab,ti OR 'local application':ab,ti OR intrawound:ab,ti OR 'intra wound':ab,ti OR intrasite:ab,ti OR 'intra site':ab,ti OR powder:ab,ti OR vancomycin:ab,ti OR gentamicin:ab,ti OR gentamycin:ab,ti OR dermacyn:ab,ti OR iodine:ab,ti OR 'povidone iodine':ab,ti OR 'PVP I':ab,ti OR betadine:ab,ti OR chlorhexidin*:ab,ti OR bacitracin:ab,ti OR benzalkonium:ab,ti OR 'castile soap':ab,ti OR 'anti infectant':ab,ti OR antiseptic*:ab,ti OR surfactant*:ab,ti OR microbicides:ab,ti) AND [embase]/lim NOT [medline]/lim	563
Cochrane library	("surgical wound infection":ab,ti,kw OR "surgical site infection":ab,ti,kw OR SSI:ab,ti OR "joint infection":ab,ti OR "deep infection":ab,ti OR "postoperative wound	627

(continued)

Database	Search Syntax	Results
	infection":ab,ti) AND ("local administration":ab,ti OR "local application":ab,ti OR intrawound:ab,ti OR intra-wound:ab,ti OR intrasite:ab,ti OR intra-site:ab,ti OR powder:ab,ti OR vancomycin:ab,ti OR gentamicin:ab,ti OR gentamycin:ab,ti OR dermacyn:ab,ti OR iodine:ab,ti OR povidone-iodine:ab,ti OR PVP-I:ab,ti OR betadine:ab,ti OR chlorhexidin*:ab,ti OR bacitracin:ab,ti OR benzalkonium:ab,ti OR "castile soap":ab,ti OR anti-infect*:ab,ti OR antiseptic*:ab,ti OR surfactant*:ab,ti OR microbicides:ab,ti)	

Authors' Note

No ethical committee approval was deemed necessary for this systematic review and meta-analysis.

Declaration of Conflicting Interests

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