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■ INFECTION

Efficacy and safety of intrawound vancomycin in primary hip and knee arthroplasty

A SYSTEMATIC REVIEW AND META-ANALYSIS: IMPLICATIONS FOR THE DESIGN OF A RANDOMIZED CONTROLLED TRIAL

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Aims

The efficacy and safety of intrawound vancomycin for preventing surgical site infection in primary hip and knee arthroplasty is uncertain.

Methods

A systematic review of the literature was conducted, indexed from inception to March 2020 in PubMed, Web of Science, Cochrane Library, Embase, and Google Scholar databases. All studies evaluating the efficacy and/or safety of intrawound vancomycin in patients who underwent primary hip and knee arthroplasty were included. Incidence of periprosthetic joint infection (PJI), superficial infection, aseptic wound complications, acute kidney injury, anaphylactic reaction, and ototoxicity were meta-analyzed. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs). The quality of included studies was assessed using the risk of bias in non-randomized studies of interventions (ROBINS-I) assessment tool.

Results

Nine studies involving 4,607 patients were included. Intrawound vancomycin was associated with lower incidence of PJI (30 patients (1.20%) vs 58 control patients (2.75%); OR 0.44, 95% CI 0.28 to 0.69) and simultaneous acute kidney injury (four patients (0.28%) vs four control patients (0.35%), OR 0.71, 95% CI 0.19 to 2.55). However, it did not reduce risk of superficial infection (four patients (0.67%) vs six control patients (1.60%), OR 0.60, 95% CI 0.17 to 2.12) and was associated with higher incidence of aseptic wound complications (23 patients (2.15%) vs eight in control patients (0.96%), OR 2.39, 95% CI 1.09 to 5.23). Four studies reported no anaphylactic reactions and three studies reported no ototoxicity in any patient group.

Conclusion

The current literature suggests that intrawound vancomycin used in primary hip and knee arthroplasty may reduce incidence of PJI, but it may also increase risk of aseptic wound complications.

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Keywords: Vancomycin, Intrawound, Arthroplasty, Hip, Meta-analysis, Knee

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Article focus

- Can intrawound vancomycin reduce risk of periprosthetic joint infection (PJI) in patients after primary hip and knee arthroplasty?
- Can intrawound vancomycin reduce risk of superficial infection?
- Does intrawound vancomycin increase the risk of aseptic wound complications and other adverse events?

Key messages

- Intrawound vancomycin used in primary hip and knee arthroplasty may reduce incidence of PJI.
- Intrawound vancomycin did not reduce the risk of superficial infection.
- Intrawound vancomycin may increase risk of aseptic wound complications.

Strengths and limitations

- This is the first systematic review and meta-analysis assessing both the efficacy and safety of intrawound vancomycin treatment in primary hip and knee arthroplasty.
- The primary studies included in our analyses are of poor quality, which may affect our results.
- The included studies varied in recruitment period, follow-up time, dosage, sites of application, and vancomycin formulation.

Introduction

Surgical site infection (SSI), including superficial infection and periprosthetic joint infection (PJI), is a catastrophic complication after total hip arthroplasty (THA), total knee arthroplasty (TKA), and unicompartmental knee arthroplasty (UKA). It is a significant challenge for patients, surgeons, and healthcare providers. It not only delays functional rehabilitation, but also prolongs postoperative length of stay to facilitate intravenous antibiotics and is associated with increased morbidity and mortality.[1,2] National data from both the UK and the USA showed that the incidence of PJI varies from 0.4% to 2% after THA[3] or TKA.[4] An estimated 40,000 to 80,000 patients each year will suffer from PJI following hip and knee arthroplasty by 2030 in the USA.[5]

Administration of intravenous antibiotics, typically cephalosporins such as cefazolin and cefuroxime,[6] is initiated before a skin incision is made in order to significantly reduce risk of PJI.[7] However, as many as 60% of wound infection isolates cultured from joint arthroplasties in the USA are resistant to cephalosporins.[8-10] This includes the two most common bacteria causing deep infection, methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus*. Hence, local use of antibiotics that are effective against these bacteria, for example vancomycin, may be beneficial.

Vancomycin kills gram-positive bacteria by inhibiting the production of phospholipids and peptides in cell walls at the trans-glycosylation stage.[11] A meta-analysis including 27 studies of 17,321 patients showed that intrawound application of vancomycin can reduce SSI in various spinal surgeries.[12] The available studies for primary hip and knee arthroplasty have given inconsistent results.[13,14] Although local use of antibiotics is considered safer than intravenous application, local and systematic adverse reactions, such as aseptic wound complications, anaphylactic reaction, ototoxicity, wound healing, and kidney function, must be considered. In addition, the International Consensus on Orthopaedic Infections offers only a limited recommendation for intrawound administration of vancomycin during arthroplasty procedures.[15]

This systematic review and meta-analysis was conducted to assess the safety and efficacy of intrawound vancomycin in reducing risk of PJI and superficial infection in patients after primary hip and knee arthroplasty.

Methods

This systematic review and meta-analysis followed the methodology proposed by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Table i). It also had been registered at International Prospective Register of Systematic Reviews (CRD42020175679).

Search strategy and eligibility criteria. We conducted a comprehensive literature search across the electronic databases of PubMed, Web of Science, Cochrane Library, Embase, and Google Scholar, from their inception to March 2020. Three groups of keywords or medical subject headings were used in our queries: 'vancomycin' OR 'vancomycin powder' OR 'antibiotic' AND 'local' OR 'topical' OR 'intrawound' OR 'intra-wound' AND 'arthroplasty' OR 'knee arthroplasty' OR 'hip arthroplasty' OR 'arthroplasty' OR 'knee arthroplasty' OR 'hip arthroplasty'. The vocabulary and keyword combinations were adjusted for each database. Two reviewers (HX and JY) manually and independently reviewed all the retrieved literature, and any disagreements were resolved by discussion with a third reviewer (JX).

To be eligible for inclusion, studies must have assessed the efficacy and safety outcomes from intrawound administration of vancomycin after primary hip and knee arthroplasty to prevent PJI and superficial infection. Studies were excluded if they did not include controls (who underwent surgery but did not receive local vancomycin), case reports, commentaries, expert opinions, or reviews, or if animals were used instead of humans. Furthermore, all references cited in these included studies and relevant review articles were screened manually. No language restrictions were applied during the literature search.

Data extraction. Two reviewers independently extracted relevant data from the included studies using a standardized form from March 2020. The following data were collected from each study: 1) the characteristics of each included study, including study design, location and name of study site, type of surgery, the dose and site of vancomycin administration, drain usage, details of intravenous antibiotics, and the definitions of PJI, superficial infection, aseptic wound complications, and acute kidney injury; and 2) the characteristics of populations involved in each included study, including their number, sex, age, and body mass index (BMI), recruitment period and follow-up time, and comorbidities such as diabetes, hypertension,

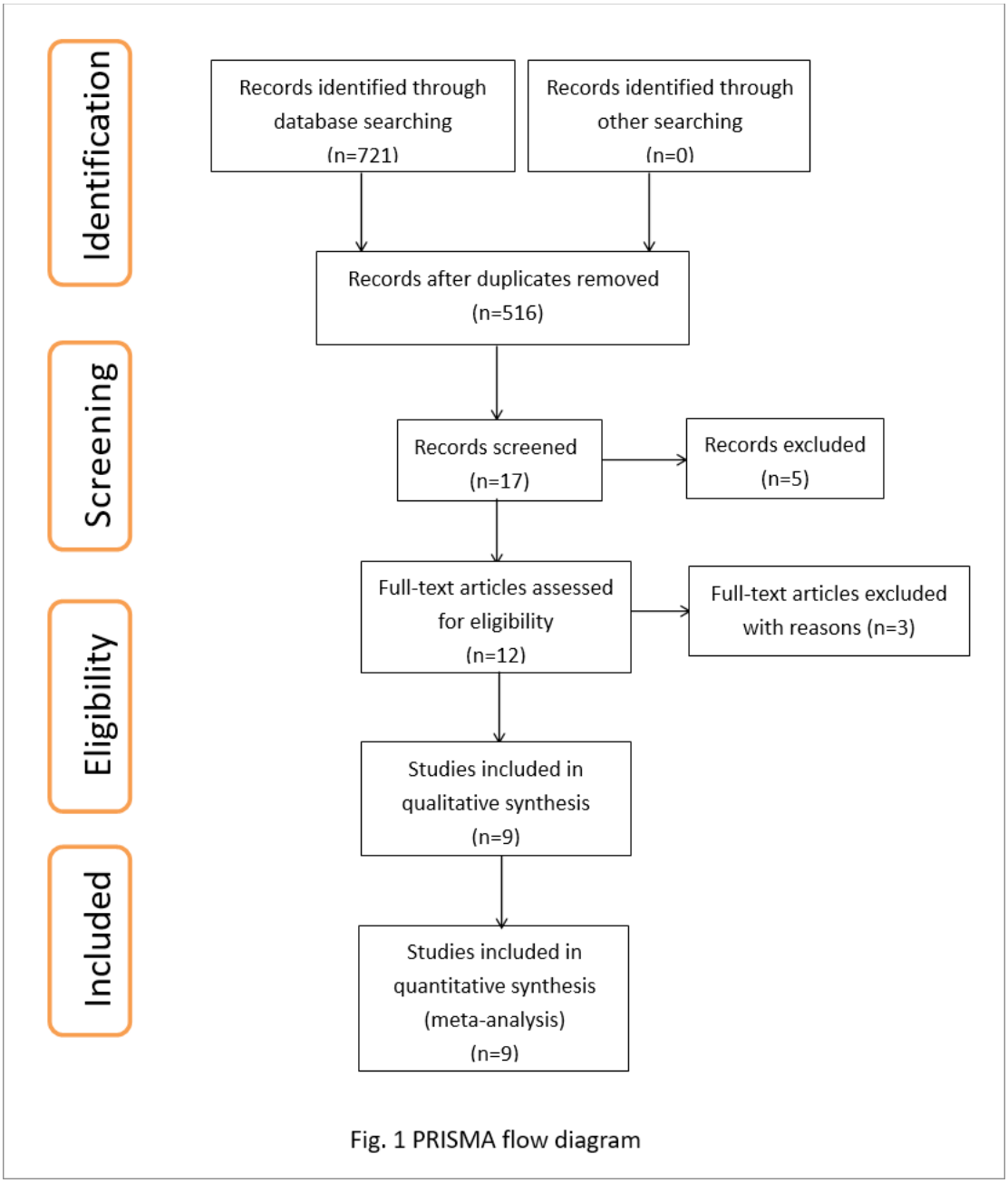

Fig. 1

Flow diagram of literature searching and study inclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

chronic obstructive pulmonary disease or pulmonary disease, and chronic kidney disease. Outcomes included the incidence of PJI, superficial infection, aseptic wound complications, acute kidney injury, anaphylactic reaction, and ototoxicity.

Quality assessment. The quality of the included studies was assessed using the risk of bias in non-randomized studies of interventions (ROBINS-I) assessment tool. This tool comprises seven domains: the first and second domains address 'baseline' issues, such as confounding factors and selection of participants, which involve comparisons before the start of the intervention. The third domain addresses classification of the interventions, and the other four domains address biases arising after the start of the intervention, such as deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results. The risk of bias within each domain is determined based on their 'signalling questions'. The overall bias risk of each study is classified as 'low', 'moderate', 'serious', 'critical', or 'no information', which is determined according to the results for the seven domains.[16] In our study, individual domains

and overall risk of bias assessment was performed independently by two reviewers for each included study. Any discrepancies were resolved by discussion with a third reviewer.

Statistical analysis. All statistical analyses were performed using Stata 11 (StataCorp, College Station, Texas, USA). Heterogeneity across studies was assessed using the inconsistency index (I^2). Briefly, this analysis estimates the percentage of the variability in results from multiple studies that is likely due to true differences in outcomes, study design, patients, and tests, rather than to sampling error.[17] Heterogeneity was considered 'low' if I^2 was 25%, 'moderate' if I^2 was 50%, or 'high' if I^2 was 75%.[18] All meta-analyses were performed using a fixed-effect model because I^2 was less than 25% for all outcomes assessed.[19]

Pooled results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) where appropriate. Publication bias was assessed using a funnel plot[20] and Egger's test.[21] Significant publication bias was considered if the associated p-value was less than 0.05.

Results

Search results. Our systematic search retrieved 721 literature records, of which 516 remained after removing duplicates. Studies were first assessed based on their title and abstract, which led to 12 studies that were then read in full. We excluded three studies for the following reasons: in one study, both the intravenous and local antibiotic regimens among patients were inconsistent,[22] one lacked a control group,[23] and one lacked specific data of infection patients.[24] Finally, nine studies were included in the meta-analysis (Figure 1). Two studies[25,26] examined patients who underwent primary or revision THA and TKA, but we excluded the participants who underwent revision procedures due to increased risk of infection.[13]

Characteristics of included studies and participants. All included studies were retrospective with the exception of one prospective study (Table I).[27] A total of 4,607 patients were included in our analyses, comprising 2,497 patients treated with intrawound vancomycin and 2,110 controls (Table II). All included studies reported the definition of PJI: four[13,28-30] of them determined the PJI based on the International Consensus Meeting (2013);[31] two,[25,26] based on the Musculoskeletal Infection Society (2011) criteria;[32] one, based on treatment method;[33] one, based on articular fluid culture;[27] and one,[14] based on Musculoskeletal Infection Society (2011) criteria and culture. Only one study[30] included patients who underwent UKA (n = 26). While a majority of studies used vancomycin alone in soft tissue, some studies employed other methods: one study included surgical intervention that coated 1 g of vancomycin onto the acetabular and femoral components immediately before implantation;[29] and in another study, 1 g to 2 g of vancomycin powder was combined with 2 g of an absorbable calcium hydroxyapatite, and then the mixture was spread in a thin layer on the articular surface of the implants before implantation.[27]

Table I presents further study characteristics, including the dose of vancomycin intervention, drain use, details of intravenous antibiotics, and definitions of PJI, superficial infection, and acute kidney injury. The recruitment period differed for patients treated with intrawound vancomycin and controls in all but two studies.[27,33] Follow-up time was different between the two groups in two studies,[14,30] and one study[25] did not report follow-up time. Table II describes patient characteristics including sex, age, BMI, and comorbidities.

Quality assessment and publication bias of included studies. In general, the quality of included studies was unsatisfactory (Table III). Three studies[29,33] were considered to have 'moderate' risk of bias and another six studies[13,14,25,26,28,30] were at 'serious' risk of bias. We believe this is due to the retrospective nature and substantial confounding bias. In contrast, according to the funnel plot analysis and the result of Egger's test (t = -1.550; p = 0.165), we detected no observable publication bias across all included studies (Figure 2).

Efficacy of intrawound vancomycin application. PJI was reported for all participants in the included studies, so data were pooled from all studies. A total of 30 (1.20%) patients in the vancomycin group and 58 (2.75%) in the control group developed PJI, respectively; meta-analysis indicated an OR for PJI of 0.44 (95% CI 0.28 to 0.69) when intrawound vancomycin was used, with no study heterogeneity observed (I^2 = 0.0%) (Figure 3a). Four studies[14,27,30,33] reported superficial infections in 598 patients treated with intrawound vancomycin and 377 in the control group. The incidence of superficial infection between the patients receiving intrawound vancomycin and control group showed no difference: four (0.67%) versus six (1.60%), with meta-analysis giving a pooled OR of 0.60 (95% CI 0.17 to 2.12) with no study heterogeneity (I^2 = 0.0%) (Figure 3b).

Safety of intrawound vancomycin administration. We also analyzed the incidence of adverse events associated with intrawound administration of vancomycin. Four studies[13,14,28,30] reported that aseptic wound complications occurred in 1,069 treated patients (23 with aseptic wound complications, 2.15%) and 834 control patients (eight with aseptic wound complications, 0.96%). Meta-analysis confirmed that intrawound vancomycin treatment was associated with higher risk of aseptic wound complications (OR 2.39, 95% CI 1.09 to 5.23), with no substantial heterogeneity observed across the studies (I^2 = 16.2%) (Figure 3c). Moreover, the study performed by Hanada et al[28] reported that three out of five patients who suffered from PJI in the vancomycin group had aseptic wound complications within three months after primary surgery in their subjects. Additionally, they also revealed that intrawound vancomycin treatment may be related to higher risk of prolonged healing of wound (> two weeks): 14 (12.7%) versus three (3.3%) (OR 4.32, 95% CI 1.20 to 15.56; p = 0.016). The definition, number of patients, treatment measures, and outcomes of aseptic

Table I. Characteristics of studies included in the meta-analysis.

Study	Location	Study design	Surgery	Intervention	Definition of PJI	Definition of superficial infection	Definition of acute kidney injury	Drain use	Intravenous antibiotic
Yavuz et al[13] 2019	Univ. of Health Science, Ankara Numune Training and Research Hospital, Ankara, Turkey	R	Primary TKA	2 g VP / joint capsule	ICM (2013)[34]	NR	NR	24 hrs post-op	2 g cefazolin / 30 mins before incision
Hanada et al[28] 2019	Hamamatsu University School of Medicine, Hamamatsu, Japan	R	Primary TKA or UKA	1 g VP / intracapsular	ICM (2013)	NR	NR	1 or 2 days post-op	2 g cefazolin before incision, 1 g once every 6 hrs on the day of surgery
Cohen et al[29] 2019	Rhode Island Hospital, Providence, Rhode Island, USA	R	Primary THA	1 g VP / coat the acetabular and femoral components	ICM (2013)	NR	NR	No drain	1 dose pre-op and 2 doses post-op cefazolin (weight-based)
Dial et al[30] 2018	Duke University Medical Center, Durham, North Carolina, USA	R	Primary THA	1 g VP / intracapsular and extracapsular	ICM (2013)	Surgical site infections that resolved with oral antibiotics	An increase in serum creatinine greater than 0.3 mg/dl	NR	Cefazolin (2 g) started prior to skin incision and 1 dose 24 hrs post-op
Patel et al[14] 2018	Emory University School of Medicine, Atlanta, Georgia, USA	R	Primary THA and TKA	1 g VP / joint, muscle, fascia, subcutaneous tissues	MSIS or single positive culture	Culture-positive of superficial wound	Increase of > 0.3 mg/dl in serum creatinine post-op	NR	1 dose cephalosporin/ within 1 hr before incision
Winkler et al[25] 2018	Texas Tech University Health Sciences Centre, Lubbock, Texas, USA	R	Primary THA and TKA	2 g VP / joint capsule	MSIS (2011)[32]	NR	Identified by blood urea, nitrogen, and creatinine values	Dressed with an incisional wound vacuum	Cefazolin/1 dose pre-op followed by 3 doses post-op
Khatri et al[33] 2017	Multicentre, India	R	Primary TKA	1 g VP / subfacial layer	Infection treated by debridement, intravenous antibiotics, even two-stage revision	Infection managed with oral antibiotics	NR	No drain	1.5 g cefuroxime/ within 1 hr of skin incision and repeated every 12 hrs until drain removal
Otte et al[26] 2017	Mount Carmel Health Systems, Columbus, Ohio, USA	R	Primary knee and hip arthroplasty	1 g VP / intra-articular joint space	MSIS (2011)	NR	NR	NR	Standard systemic prophylaxis
Assor[27] 2010	University of Marseille, Marseille, France	P	Primary TKA	1 g to 2 g VP mixed with 2 g hydroxyapatite / articular surface of the implants	Confirmed by articular fluid culture	NR	NR	3 or 5 days post-op	0.5 g cefazolin / used during the first 48 hrs post-op (2 g/day)

ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society; NR, not reported; P, prospective; PJI, periprosthetic joint infection; post-op, postoperatively; pre-op, preoperatively; R, retrospective; SSI, surgical site infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; VP, vancomycin.

wound complication and prolonged healing of wound are shown in Table IV.

Based on data from six studies,[13,14,28–30,33] the incidence of acute kidney injury after surgery occurred in 1,429 treated patients was 4 (0.28%) and 4 (0.35%) in 1,144 controls. Meta-analysis showed that intrawound vancomycin did not significantly alter risk of acute kidney injury (OR 0.71, 95% CI 0.19 to 2.55), with no substantial heterogeneity (I^2 = 16.6%) (Figure 3d). Additionally, anaphylactic reactions did not occur in 772 treated patients or 786 controls in studies that reported the outcome,[13,28,30,33] nor did ototoxicity occur in 595 treated patients or 332 controls in studies reporting that outcome.[14,28,30]

Discussion

To our knowledge, this is the first systematic review and meta-analysis assessing both the efficacy and safety of intrawound vancomycin treatment in primary hip and knee arthroplasty. We found that intrawound treatment may reduce the incidence of PJI without increasing risk of acute kidney injury; however, it does not reduce superficial infection but contrarily may increase risk of aseptic wound complications. Other complications, such as anaphylactic reaction and ototoxicity, are rare among patients treated with intrawound vancomycin in primary hip and knee arthroplasty. However, the reliability of the

Table II. Characteristics of patients from included studies.

Study	Group	No. of patients (male/female)	Mean age, yrs (SD)	Mean BMI , kg/m² (SD)	Recruitment period	Follow-up time	Diabetes n (%)	Hypertension n (%)	COPD or pulmonary disease, n (%)	CAD or heart disease, n (%)	Chronic kidney disease, n (%)
Yavuz et al[13] 2019	C:	502 (154/348)	63.4 (12.1)	28.9 (5.4)	2012 to February 2015	mean: 53.2 mths (24 to 84) for both groups	129 (25.6)	296 (58.9)	51 (10.2)	54 (10.8)	39 (7.8)
	V:	474 (148/326)	65.5 (10.7)	29.0 (5.7)	February 2015 to December 2016		102 (21.5)	291 (61.4)	53 (11.2)	41 (8.7)	27 (5.7)
	All:	976									
Hanada et al[28] 2019	C:	92 (22/70)	73.3	25.7	2010 to 2014	Not less than 1 yr for both groups	17 (18.5)	NR	4 (4.3)	12 (13.0)	6 (6.5)
	V:	110 (27/83)	74.6	26.7	2014 to 2017		22 (20)	NR	4 (3.6)	16 (14.5)	4 (3.6)
	All:	202									
Cohen et al[29] 2019	C:	246 (109/137)	67.3 (12.6)	29.2 (5.6)	April 2015 to December 2016	NR	NR	NR	NR	NR	NR
	V:	309 (149/160)	66.0 (10.2)	29.6 (5.8)	April 2015 to December 2016	NR	NR	NR	NR	NR	NR
	All:	555									
Dial et al[30] 2018	C:	128 (64/64)	61.5 (10.5)	29.8 (5.8)	June 2013 to January 2015	mean: 14.4 mths (SD 7.5)	19 (14.8)	83 (64.8)	11 (8.6)	18 (14.1)	10 (7.8)
	V:	137 (65/72)	61.2 (11.1)	30.0 (6.0)	January 2015 to February 2016	mean: 8.2 mths (SD 4.5)	16 (11.7)	83 (60.6)	4 (2.9)	23 (16)	15 (10.9)
	All:	265									
Patel et al[14] 2018	C:	112 (48/64)	64.8	31.1	April 2016 to September 2016	mean: 11.3 mths (3.0 to 25.6)	14 (12.5)	NR	NR	12 (9.8)	2 (1.8)
	V:	348 (138/210)	63.6	30.6	October 2016 to October 2017	mean: 7.7 mths (3.2 to 19.1)	34 (9.8)	NR	NR	22 (6.3)	13 (3.7)
	All:	460									
Winkler et al[25] 2018	C: TKA: THA:	152 (48/104) 97 (47/50)	27 (17.8) 63.5 (17.7)	NR	1 January 2012 to 31 December 2013	At least 6 mths for both groups	2 (1.3)	NR	14 (9.2)	40 (26.3)	NR
	V: TKA: THA:	191 (70/121) 133 (61/72)	80 (41.9) 65 (11.9)	NR	1 January 2014 to 31 December 2015		11 (5.8)	NR	24 (12.6)	50 (26.2)	NR
	All:	573									
Khatri et al[33] 2017	C:	64 (44/20)	NR	NR	February 2014 to January 2016 for two groups	6 mths for both groups	23 (35.9)	25 (39.1)	NR	NR	NR
	V:	51 (32/19)					17 (33.3)	22 (43.1)	NR	NR	NR
	All:	115									
Otte et al[26] 2017	C: TKA: THA:	392 252	NR	NR	1 May 2012 to 30 April 2013	3 mths for both groups	NR	NR	NR	NR	NR
	V: TKA: THA:	400 282	NR	NR	1 May 2013 to 30 April 2014		NR	NR	NR	NR	NR
	All:	1,326									
Assor[27] 2010	C:	73 (17/56)	72 (7.6)	NR	2002 to 2006 for both groups	mean: 5 yrs (3 to 7) for both groups	NR	NR	NR	NR	NR
	V:	62 (16/46)	73 (8.2)	NR			NR	NR	NR	NR	NR
	All:	135									

BMI, body mass index; C, control group; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NR, not reported; THA, total hip arthroplasty; TKA, total knee arthroplasty; V, vancomycin group.

available evidence is limited due to the poor quality of the included studies.

Although intravenous cephalosporins are widely used to prevent infection in primary hip and knee arthroplasty, studies report that they have no effect on more than 60% of *Staphylococcus* strains, which are the most common causes of SSIs.[10] Vancomycin is effective against many strains of pathogens, although some bacterial strains are resistant.[35] Intrawound vancomycin used in spine surgery significantly decreases risk of postoperative infection.[36] This finding likely inspired local vancomycin use in primary hip and knee arthroplasty.[37] Indeed, a previous systematic review and meta-analysis demonstrated that intrawound vancomycin may decrease the risk of PJI in primary (OR 0.44, 95% CI 0.24 to 0.77) and revision (OR 0.28, 95% CI 0.13 to 0.61) TKA and THA; however, that study did not evaluate its safety.[37] Safety risks associated with intrawound vancomycin must be taken into account, including aseptic wound complications, acute kidney injury, anaphylactic reaction, and ototoxicity. Updated, comprehensive assessment of the safety and efficacy of intrawound vancomycin in hip and knee arthroplasty is

Table III. Quality assessment of included studies

Study	Pre-intervention		At intervention	Post-intervention				Total
	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Bias across domains
Yavuz et al[13] 2019	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Hanada et al[28] 2019	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Cohen et al[29] 2019	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Dial et al[30] 2018	Serious	Moderate	Low	Moderate	Low	Low	Low	Serious
Patel et al[14] 2018	Serious	Moderate	Low	Moderate	Low	Low	Low	Serious
Winkler et al[25] 2018	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Khatri et al[33] 2017	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Otte et al[26] 2017	Serious	Moderate	Low	Moderate	Low	Low	Moderate	Serious
Assor[27] 2010	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate

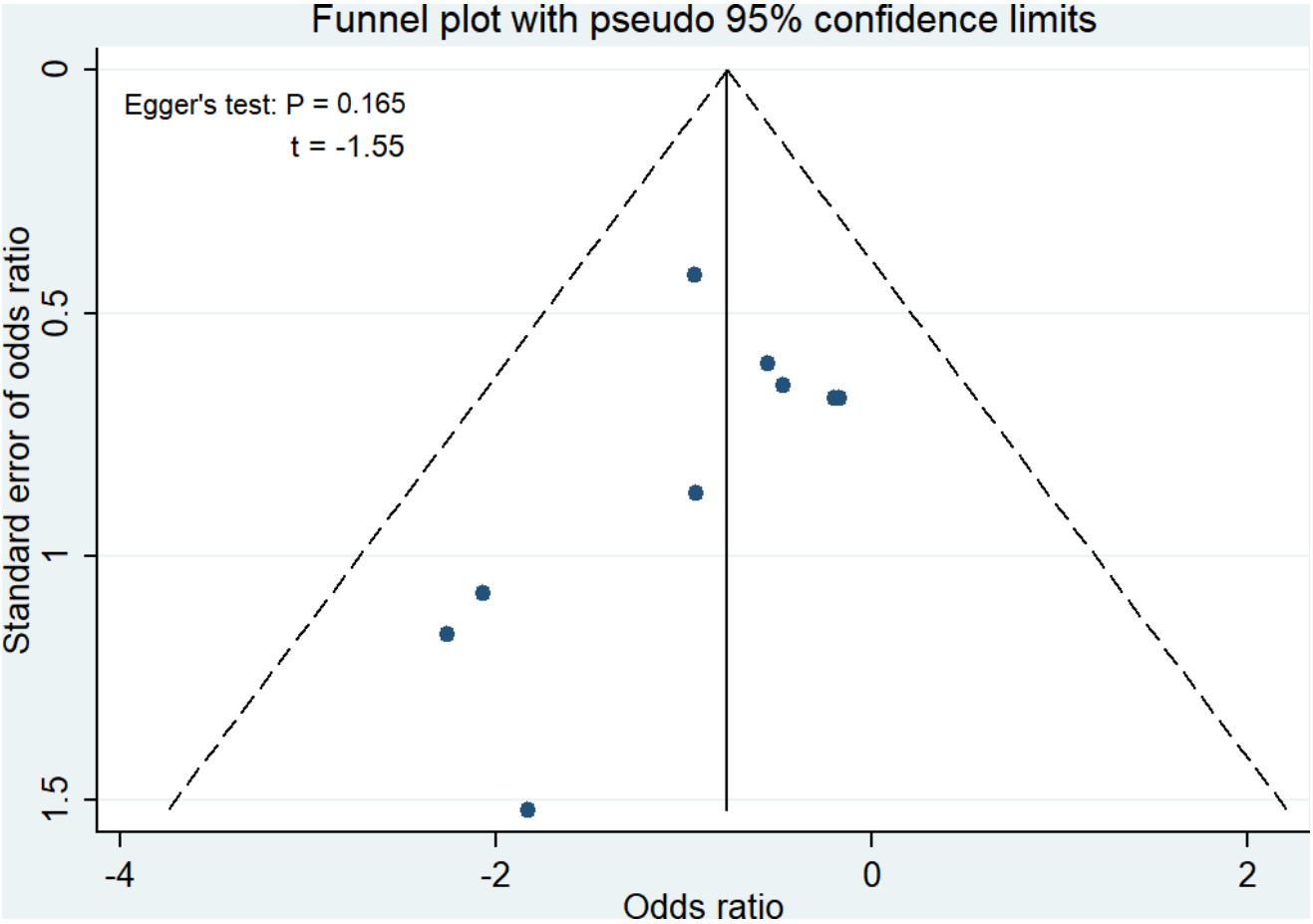

Fig. 2

Funnel plot of included studies. The dotted lines indicate pseudo 95% confidence limits.

needed in order to provide the latest evidence for this practice, especially since there are no relevant international guidelines.

A small inoculum, such as *Staphylococcus aureus* present on the skin of 15% to 25% of healthy individuals, may accrue during surgery, especially during procedures in which a foreign body is implanted, giving rise to SSIs although the skin surface is prepared beforehand and sterile technique is carefully performed.[11,38] Intrawound vancomycin was originally intended as an adjunct to intravenous prophylactic antibiotics routinely to reduce local contamination.[39] Vancomycin

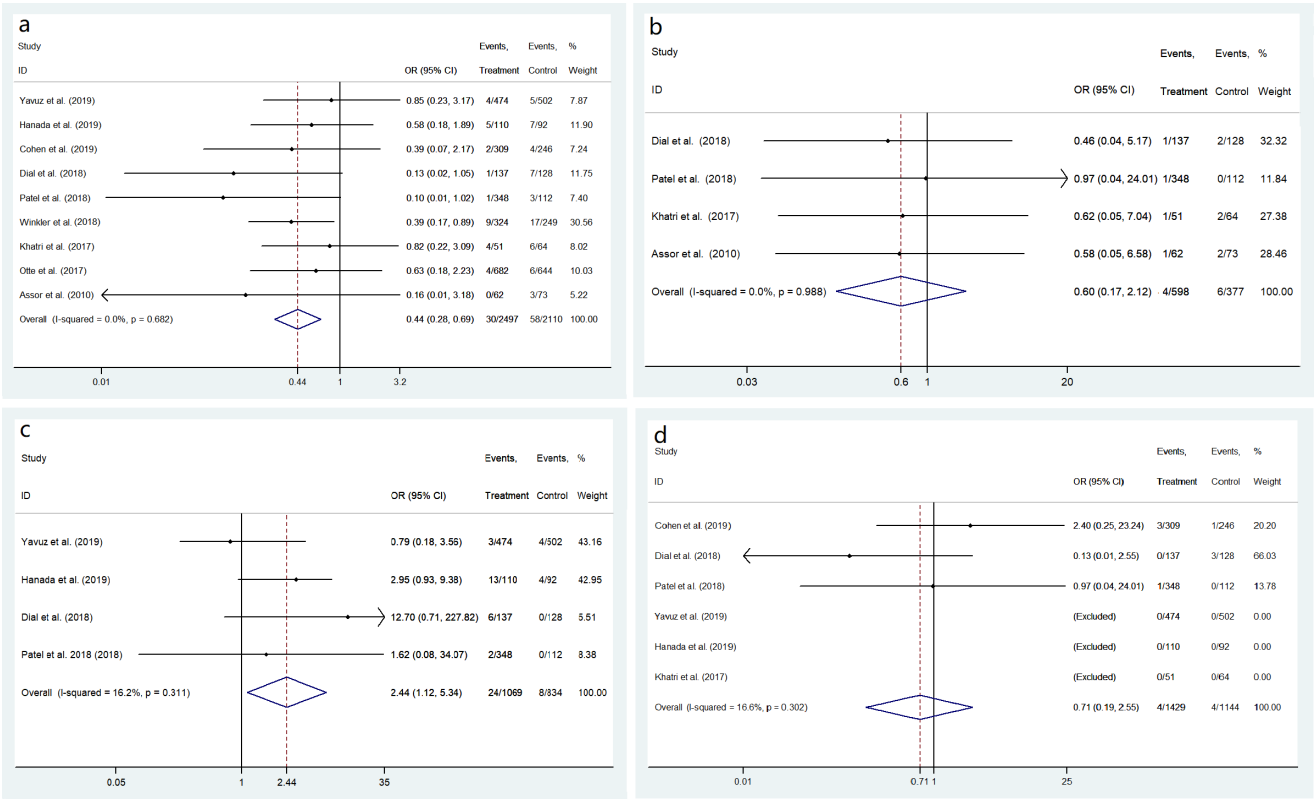

Fig. 3

Forest plots of meta-analysis of risk of a) periprosthetic joint infection, b) superficial infection, c) aseptic wound complications, and d) acute kidney injury when intrawound vancomycin was used relative to the risk without it. CI, confidence interval; OR, odds ratio.

Table IV. The details of aseptic wound complication and prolonged healing of wound of included studies.

Study	Definition of aseptic wound complication or prolonged healing of wound	No. of patients	Treatment measures	Outcomes
Yavuz et al[13] 2019	Wound bleeding during adjustment of coumadin dose	C: 4 V: 3 All: 7	Coumadin was stopped and enoxaparin was started	No PJI was observed during the follow-up
Hanada et al[28] 2019	Skin erosion and wound dehiscence	C: 4 V: 13 All: 17	3 cases in the C and 6 cases in the V required treatment by lavage and resuturing under local anaesthesia	NR
	Prolonged healing of wound (> 2 wks)* (excessive discharge, subcutaneous oedema, and seroma)	C: 3 V: 14 All: 17	3 cases in the C and 6 cases in the V required treatment by lavage and resuturing under local anaesthesia	NR
Dial et al[30] 2018	Wound breakdowns that did not meet the criteria for PJI, and required a return to the operating room for debridement and closure	C: 0 V: 6 All: 6	All patients were treated with wound debridement and closure without head or liner exchange and no postoperative antibiotics	The wounds of all 6 patients healed after debridement and closure
Patel et al[14] 2018	Stitch abscesses or erythema	C: 0 V: 1 All: 1	Irrigation and debridement, and no antibiotic was used	Healed uneventfully, and no further surgical intervention was required

*Only one study[28] reported the information of prolonged healing of wound.
C, control group; NR, not reported; PJI, periprosthetic joint infection; V, vancomycin group.

administered intravenously may damage liver and kidney functions, whereas local application restricts high drug concentrations to surgical site, thereby reducing systemic absorption and systemic side effects, such as nephrotoxicity, ototoxicity, anaphylactic reaction, and even red man syndrome.[40–42] Meta-analyses indicate that intrawound application of vancomycin significantly reduces SSI rate both in spinal surgery (OR

0.31, 95% CI 0.19 to 0.50)[12] and non-spinal neurosurgery (OR 0.25, 95% CI 0.12 to 0.52).[43] Similarly, our results also associate intrawound application of vancomycin with lower PJI in primary hip and knee arthroplasty (OR 0.44, 95% CI 0.28 to 0.69). However, we note that most of the studies in these three meta-analyses were retrospective, and their quality was poor.

The safety of intrawound application of vancomycin in primary hip and knee arthroplasty is a major concern for surgeons.[44] Our study reinforces this concern by showing that intrawound vancomycin (1 g to 2 g) increases the risk of aseptic wound complications, including wound bleeding, skin erosion, wound dehiscence, seroma, and stitch erythema. Correspondingly, this may associate with the higher risk of reoperative including lavage or irrigation, debridement, and re-suturing.[28,30] Another study showed that intrawound application of vancomycin can delay wound healing,[35] which was in line with the study performed by Hanada et al.[28] Hoelen et al[45] reported that vancomycin may cause local non-bullous skin necrosis if it leaks into the surrounding tissues from veins due to vancomycin solution having a low pH (2.8 to 4.5), which has a direct irritant effect on the vascular wall. Although the cause of aseptic wound complications is uncertain, these may result, at least in part, from a direct release of histamine by vancomycin or coproducts, local inflammatory response triggered by impurities in the vancomycin itself, or by the body's response to vancomycin and/or impurities.[29]

The risk of positively selecting drug-resistant organisms is another concern that has prevented broader application of intrawound vancomycin in arthroplasty.[39] Johnson et al[46] reported that vancomycin could be present in treated tissue at concentrations over 200 µg/ml for 24 hours postoperatively after local administration of 2 g of vancomycin, much higher than the concentrations of 15 µg/ml to 20 µg/ml recommended for life-threatening infections.[47] However, the serum level of vancomycin in that study was below 4.7 ± 3.2 µg/ml, which is subtherapeutic and may lead to emergence of drug-resistance,[48] although an association between local administration of antibiotic and emergence of resistant bacteria has been difficult to demonstrate. In addition, the potential for third body wear from crystalline vancomycin applied to the implant interface may promote degradation of the implant. Nevertheless, simulations by Qadir et al[49] suggest that local crystalline of vancomycin does not alter wear rates of cobalt-chromium (Co-Cr) on ultra-high molecular weight polyethylene, which may reflect the short half-life of vancomycin (7.2 hours) in the intra-articular space.[46] These considerations make clear that intrawound vancomycin, while offering clinical benefits, should be further optimized.

While we found no systemic adverse events from intrawound application of vancomycin, such as acute kidney injury, ototoxicity, or anaphylactic reaction, only a subset of included studies reported these outcomes. This lack of adverse events may reflect the benefits of local administration, although the vancomycin is ultimately excreted through the kidneys.[50] In addition, some surgeons are concerned that high local vancomycin levels may affect bone healing.[51] Edin et al[52] suggested that local vancomycin of therapeutic concentration has no obvious impact on osteoblast replication. In fact, that study concluded that vancomycin may be even less toxic to osteoblasts than cefazolin. On the other hand, Chu et al[53] reported that vancomycin has dose-dependent toxic effects on mesenchymal stem cells (MSCs) in vitro: incubation for 24 hours in medium containing 400 µg/ml or 1,600 µg/ml vancomycin led to MSC death rates of 9.43% and 13.79%, respectively. Consequently, higher doses of local vancomycin may not bring additional benefits, and optimal dosing needs to be further explored.

Our meta-analysis should be interpreted with caution given the limitations of the available literature. The studies included in our analyses being of poor quality will impact the results. In addition, the included studies varied in recruitment period, follow-up time, dosage, sites of application, and vancomycin formulation, and these variations may create biases and affect our results. Finally, future prospective high-quality studies are needed to verify our results, especially for the impact of intrawound vancomycin on aseptic wound complication including its dose, site of use, and the size of the wound. However, due to the low incidence of PJI, about 1,000 patients undergoing primary hip and knee arthroplasty are required to conform a large decrease in PJI from 2.74% to 1.00% in control versus vancomycin groups, with a power of 80% and at a 5% significance level in a randomized controlled trial (RCT).

In conclusion, intrawound application of vancomycin may decrease the risk of PJI but concurrently increase the risk of aseptic wound complications in primary hip and knee arthroplasty. More high-quality RCTs should be performed to clarify the advantages or disadvantages of intrawound vancomycin due to the poor quality of the included studies.

Supplementary material

Table showing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

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