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KNEE ARTHROPLASTY

Safety and effectiveness of intraosseous regional prophylactic antibiotics in total knee arthroplasty: a systematic review and meta-analysis

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Abstract

Background Intraosseous regional administration (IORA) as a widely applicable and clinically valuable route of administration has gained significant attention in the context of total knee arthroplasty (TKA) for the prophylactic administration of antibiotics. However, there is still controversy regarding its effectiveness and safety. The latest meta-analysis reports that the use of IORA for antibiotics in TKA is as safe and effective as IV administration in preventing prosthetic joint infection (PJI), but they did not separate the statistics for primary TKA and revision TKA, which may be inappropriate. There is currently a lack of evidence specifically comparing the outcomes of prophylactic antibiotic administration via IORA or IV route in primary/revision TKA, respectively, and new research evidence has emerged.

Purposes In this study, we conducted a systematic review and meta-analysis with the primary objective of comparing the local drug tissue concentration and the incidence of PJI between preoperative IORA and intravenous (IV) administration of prophylactic antibiotics in TKA. Additionally, the occurrence of complications between the two administration routes was also compared.

Patients and Methods This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) guidelines. Retrospective cohort studies and prospective randomized controlled trials that utilized intraosseous local drug delivery for prophylactic antibiotics in knee arthroplasty were included. English literature from PubMed, Embase, and Cochrane Library databases was searched from the inception of each database until December 2023. Two researchers independently screened the literature, assessed the quality, and extracted data according to the inclusion criteria. The primary outcomes were local antibiotic tissue concentration and postoperative PJI incidence, while the secondary outcome was the occurrence of postoperative complications. Statistical analysis was performed using Review Manager 5.3 software.

Results This study included 7 prospective randomized controlled trials and 5 retrospective cohort studies. A total of 4091 patients participated in the 12 included studies, with 1,801 cases receiving IORA and 2,290 cases in the control group. In terms of local drug tissue concentration, intraosseous infusion (IO) 500 mg vancomycin significantly increased the drug concentration in the periarticular adipose tissue (SMD: 1.36; 95% CI: 0.87–1.84; $P < 0.001$; $I^2 = 0\%$) and bone tissue (SMD: 0.94; 95% CI: 0.49–1.40; $P < 0.001$; $I^2 = 0\%$) compared to IV 1 g vancomycin. Regarding the incidence of postoperative PJI after primary TKA, IO 500 mg vancomycin was more effective in reducing the occurrence of PJI compared to IV 1 g vancomycin (OR: 0.19; 95% CI: 0.06–0.59; $P < 0.001$; $I^2 = 36\%$). Finally, no significant differences were found between the two groups in terms of postoperative pulmonary embolism (PE) (OR: 1.72; 95% CI: 0.22–13.69; $P = 0.59$; $I^2 = 0\%$) and vancomycin-related complications (OR: 0.54; 95% CI: 0.25–1.19; $P = 0.44$; $I^2 = 0\%$).

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Conclusions Preoperative prophylactic antibiotic administration via IORA in TKA significantly increases local drug tissue concentration without significantly increasing systemic drug-related complications compared to traditional IV administration. In primary TKA, low-dose vancomycin via IORA is more effective in reducing the incidence of PJI compared to traditional IV regimens. However, its effectiveness remains controversial in high-risk populations for PJI, such as obese, diabetic, and renal insufficiency patients, as well as in revision TKA.

Keywords Total knee arthroplasty · Intraosseous · Antibiotic · Prosthetic joint infection

Introduction

Total knee arthroplasty (TKA) is one of the most successful surgical procedures of the twentieth century and is considered the gold standard treatment for end-stage knee osteoarthritis [1]. The number of TKAs performed in the United States has been steadily increasing [2]. However, complications such as infection, pain, anemia, and thromboembolism still occur in the early postoperative period of TKA [3]. Prosthetic joint infection (PJI) is considered a "catastrophic" complication following TKA. Some researchers have attempted prophylactic antibiotic using foot vein catheterization with a tourniquet to reduce venous reflux and limit drug distribution in the target limb, in order to achieve higher tissue concentration and reduce the incidence of PJI in TKA. [4]. Although foot vein catheterization can be challenging and may increase the risk of infection [5], the use of a tourniquet provides a new direction for perioperative drug administration in TKA by confining the drugs to the target limb.

Intraosseous infusion (IO) is a method of drug administration that utilizes the rich vascular network in the bone marrow cavity of long bones to deliver drugs and fluids into the bloodstream. In 1916, Drinker et al. [6] demonstrated through animal experiments that IO could be an effective alternative to intravenous (IV) infusion when peripheral vascular conditions are poor. Several studies have shown that IO can achieve pharmacokinetics and pharmacodynamics similar to those of peripheral vascular administration [7, 8]. In recent years, the IO route has also gained attention from orthopedic surgeons, and by combining the IO route with tourniquet techniques, it may be possible to achieve higher tissue concentrations than systemic administration.

Compared to traditional IO techniques, the currently used intraosseous regional administration (IORA) for local drug delivery has two main differences. Firstly, limb ischemia is generally considered a contraindication for IO, but IORA is performed after exsanguination and tourniquet inflation [9]. Secondly, IORA is typically administered by bolus injection rather than infusion [10]. This is done to ensure that the drug primarily acts locally before entering the systemic circulation through the intraosseous vascular network. In theory, long bones with prominent bony landmarks such as the humeral head, proximal and distal tibia, sternum, clavicle, and calcaneus can be used to establish an intraosseous route [11].

Young et al. [5] first achieved satisfactory results by administering antibiotics via IORA in TKA in 2013. As a promising and clinically important route of administration, the prophylactic use of IORA for antibiotics in TKA has gained attention. However, it should be noted that IORA may lead to complications such as drug extravasation, bone injury, osteomyelitis, or compartment syndrome. A systematic review has indicated that the local antibiotic concentration after preoperative IORA in TKA is approximately ten times higher than that achieved with IV administration alone. However, they did not analyze the impact of IORA antibiotics on the incidence of PJI, nor did they conduct statistical analysis.[12]. The latest meta-analysis also suggests that the use of IORA for antibiotics in TKA is as safe and effective as IV administration in preventing PJI. It is reported that the incidence of PJI in revision TKA is significantly higher than that in primary TKA, but they did not separate the statistics for primary TKA and revision TKA, which may be inappropriate.[13]. There is currently a lack of evidence specifically comparing the outcomes of prophylactic antibiotic administration via IORA or IV route in primary/revision TKA, respectively, and new research evidence has emerged. Therefore, we conducted this systematic review and meta-analysis to comprehensively compare the existing evidence on IORA and IV antibiotics in TKA.

Methods

Literature sources and search strategy

A primary search for relevant studies was conducted in the following electronic databases, including PubMed, EMBASE, and the Cochrane Library, from inception to December 2023. The search strategy used MeSH headings such as 'Arthroplasty, Replacement, Knee', 'Anti-Bacterial Agents', and 'Administration, Topical'. As well as keywords such as 'knee replacement', 'knee arthroplasty',

'intraosseous', 'intraosseous infusion', 'intraosseous inject' and 'intraosseous regional administration'. The specific retrieval strategy can be found in Supplementary 1. No limitation was applied to language or publication status. Besides, all relevant publications and review, reference lists were manually searched to identify potential studies.

Inclusion and exclusion criteria

This review included relevant clinical studies that utilized intraosseous local drug delivery techniques for prophylactic antibiotics in knee arthroplasty. The inclusion criteria were as follows: (1) clinical studies related to the use of intraosseous local antibiotics in knee arthroplasty, and (2) study designs including randomized controlled trials, cohort studies, case–control studies, and case series. The exclusion criteria were as follows: (1) literature not related to intraosseous drug administration in total knee arthroplasty, (2) animal experiments, (3) duplicate publications, (4) literature inaccessible in full-text, and (5) non-English literature. This systematic review was not registered in the randomized controlled trial (RCT) database, but the search process followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA).

Outcome assessments

The primary outcomes of the study were the local tissue drug concentrations and the postoperative PJI rate, comparing the use of preoperative prophylactic antibiotics via IORA or IV administration in TKA. The secondary outcomes included the occurrence rates of complications such as puncture-related complications and drug-related complications.

Screening and selection process

Two authors independently reviewed the full texts by screening the titles and abstracts to determine the inclusion of the literature. Any discrepancies were resolved by consulting a third author, and a consensus was reached through discussion among the three authors.

Data collection

The following specific information was extracted from the included literature: first author, country, study date; study design and objectives; characteristics of the study population; sample size; study outcomes and the standards/scores used for quantification; and complications.

Literature quality assessment

Two authors independently assessed the quality of the included RCTs using the Cochrane Risk of Bias assessment tool. For non-RCT studies, we used the Risk of Bias in Non-Randomized Studies of Intervention (ROBINS-I) tool to assess the quality of evidence for each study. In case of disagreement between the two authors, consensus was reached through discussion.

Statistical analysis

Statistical analysis was performed using Review Manager 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, 2014, Copenhagen, the Netherlands). Heterogeneity was evaluated using the Q test and I^2 statistic. If no significant heterogeneity was found ($P > 0.1$ and $I^2 < 50\%$), the data were pooled using a fixed-effects model. If significant heterogeneity was present ($P < 0.1$ or $I^2 > 50\%$), a random-effects model was used. For continuous variables, standardized mean differences (SMD) with their corresponding 95% confidence intervals (CI) were calculated. For categorical variables, odds ratios (OR) with their corresponding 95% CI were calculated. A p-value of < 0 0.05 was considered statistically significant for determining differences.

Results

Included studies and quality assessment

Initially, a total of 151 articles were identified through the search, and after removing duplicate records, 110 articles remained. After screening the titles and abstracts, a total of 13 articles were included. Further full-text evaluation resulted in the exclusion of one article that did not meet the criteria of this study, leaving a final total of 12 articles for analysis. The study selection process is illustrated in Fig. 1. Among them, 10 studies administered vancomycin via the IORA route, while 2 studies administered cefazolin via the IORA route. Ten studies included only primary TKA, 2 studies included only revision TKA, and 1 study included both primary and revision TKA. A total of 4091 patients participated in the 12 included studies, with 2178 cases (53.23%) being female. Of the patients, 1801 received drug administration via IORA, while 2290 were in the control group. Tables 1 and 2 summarize the characteristics of these studies.

This study included 7 RCTs, 4 retrospective cohort studies with two arms, and 1 retrospective cohort study with a single arm. The quality assessment results are detailed in Table 3. In the majority of RCT studies, the generation of random sequences and the reporting of complete data were

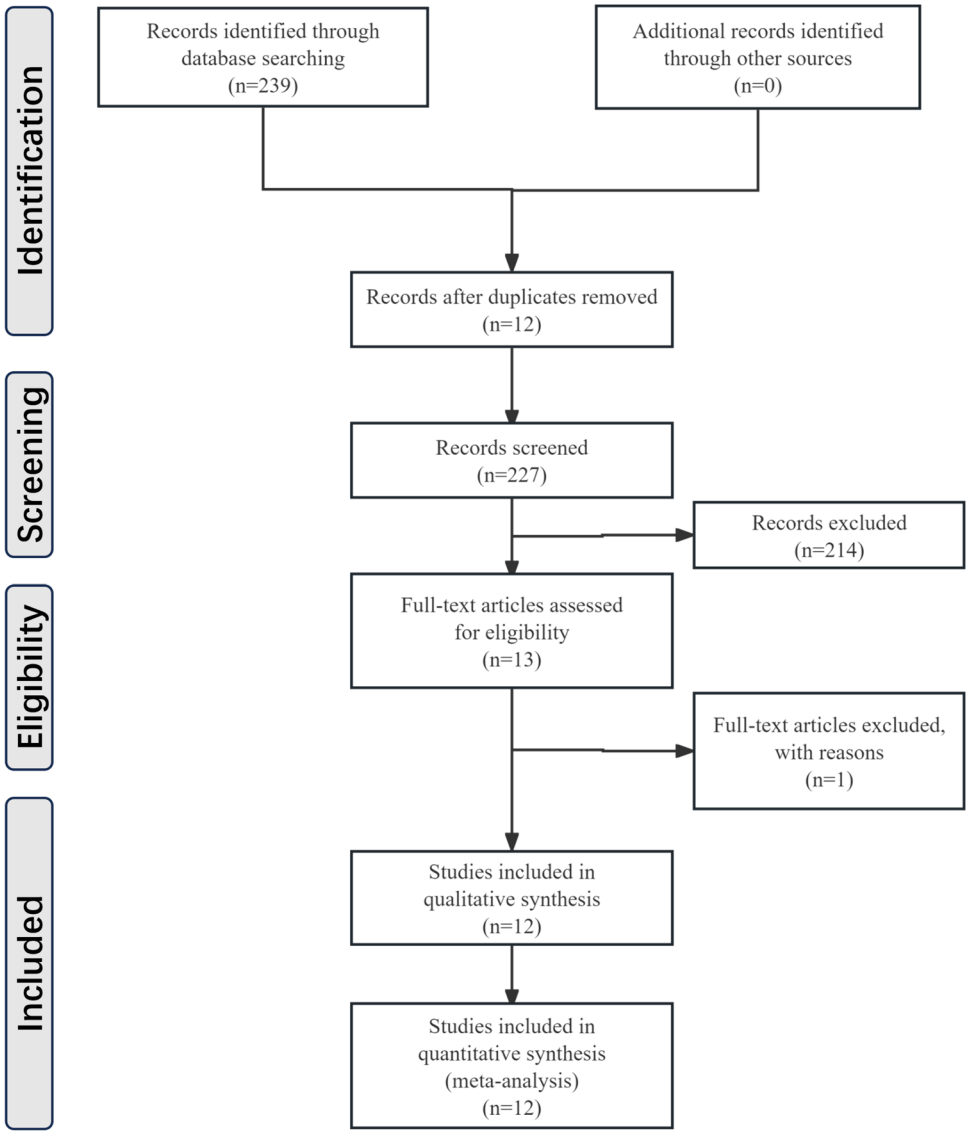

Fig. 1 The study selection process

adequately performed, while 4 studies had a high risk of bias due to the lack of blinding of investigators and participants. According to ROBINS-I, the overall bias risk of the 5 non-RCT studies was low. The quality assessment results are detailed in Table 3.

Drug concentrations in tissues

A total of 6 studies compared and reported drug tissue concentrations [5, 14–18], all of which were RCT studies. Four studies used IORA of vancomycin [14, 15, 17, 18], and 2 studies used IORA of cefazolin for preoperative prophylaxis in TKA [5, 16]. Young et al. [5] and Zhang et al. [16] compared the differences in tissue concentrations between IO and IV cefazolin. Both studies reported significant differences, but the drug doses and reported tissue concentration sites differed, preventing us from conducting a pooled analysis. The 4 studies on IORA of vancomycin compared the drug concentrations in periarticular fat and bone tissues between IO 500 mg vancomycin and IV 1 g vancomycin. The meta-analysis results showed that IO 500 mg vancomycin significantly increased the drug concentration in periarticular fat tissue (SMD: 1.36; 95% CI: 0.87–1.84; $P < 0.001$; $I^2 = 0\%$, Fig. 2) and bone tissue (SMD: 0.94; 95% CI: 0.49–1.40; $P < 0.001$; $I^2 = 0\%$, Fig. 3) compared to IV 1 g vancomycin. We intended to perform subgroup analysis for primary/revision TKA, but due to the lack of studies specifically targeting revision TKA, only one study was included [17].

Incidence of PJI

A total of 6 trials reported the incidence of PJI [14, 19–23]. The experimental group in all studies received IO 500 mg

Table 1 Characteristics and Patient Demographic of Included Studies

Study	Design	IORA						IV					
		Number	Mean Age	Woman	Average BMl	Minimum Follow-Up (Months)	Tourniquet time (minutes)	Number	Mean Age	Woman	Average BMl	Minimum Follow-Up (Months)	Tourniquet time (minutes)
Young et al. 2013 [5]	RCT	11	71.8	45.5%	27.7	N/A	84	11	65.3	63.6%	29.1	N/A	82
Young et al. 2014 [18]	RCT	10	70.8	50%	32.2	N/A	105	10	71.4	90%	34.8	N/A	99
		10	71.7	60%	30.0	N/A	102						
Chin et al. 2018 [14]	RCT	11	66	36.4%	41.1	6	N/A	11	63	45.5%	40.1	6	NA
Young et al. 2018 [17]	RCT	10	68	50%	33	N/A	129	10	69	70%	32	N/A	126
Spangehl et al. 2018	RCT	12	68	41.7%	33	N/A	25	12	69	58.3%	32	N/A	15
Zhang et al. 2023 [16]	RCT	30	68.9	80%	25.9	N/A	N/A	30	67.8	76.7%		25.6	N/A
Klasan et al. 2021 [23]	Cohort	331	67.7	58.5%	3.18	12	N/A	300	68.7	57.1%	31.4	12	N/A
Park et al. 2021 [22]	Cohort	488	67.4	58.6%	32.0	3	2 min longer than IV	572	66.7	57.7%	32.5	3	N/A
Parkinson et al. 2021 [19]	Cohort	725	67	52%	31.5	12	N/A	1181	67	49%	31.3	12	N/A
Harper et al. 2020 [20]	Cohort	119	67	36%	32	3	1.87 min longer than IV	129	67.4	46%	32	3	N/A
Lachiewicz et al. 2023 [21]	Cohort	20	67	10%	34.4	3	N/A	NO	N/A	N/A	N/A	N/A	N/A
Brozovich et al. 2022 [28]	RCT	24	65.2	62.5%	31.4	1.5	N/A	24	65.1	45.8%	30.6	1.5	N/A

N/A not available; *RCT* randomized controlled trial

Table 2 Clinical Outcomes of Included Studies

Study	Outcome	IORA			IV		
		Dosage	Outcome	Complication	Dosage	Outcome	Complication
Young et al. 2013 [5]	Tissue concentration	1g Cefazolin	Fat Concentration: 186μg/g Bone Concentration: 130μg/g	No	1g Cefazolin	Fat Concentration: 11μg/g Bone Concentration: 11μg/g	No
Young et al. 2014 [18]	Tissue concentration	250mg Vancomycin	Fat Concentration: 14μg/g Bone Concentration: 16μg/g	No	1g Vancomycin	Fat Concentration: 3.2μg/g Bone Concentration: 4.0μg/g	No
		500mg Vancomycin	Fat Concentration: 44μg/g Bone Concentration: 38μg/g	1 DVT			
Chin et al. 2018 [14]	Tissue concentration and PJI rate	500mg Vancomycin	Fat Concentration: 39.3μg/g Bone Concentration: 34.4μg/g	1 PE	15mg/kg Vancomycin	Fat Concentration: 4.4μg/g Bone Concentration: 6.1μg/g	2 superficial infections
Young et al. 2018 [17]	Tissue concentration	500mg Vancomycin	Fat Concentration: 49.3μg/g Bone Concentration: 77.1μg/g	1 Foot drop	1g Vancomycin	Fat Concentration: 3.7μg/g Bone Concentration: 6.4μg/g	No
Spangehl et al. 2018	Tissue concentration	500mg Vancomycin	Fat Concentration: 33.1μg/g Bone Concentration: 21.8μg/g	No	15mg/kg Vancomycin	Fat Concentration: 5.2μg/g Bone Concentration: 7.9μg/g	No
Zhang et al. 2023 [16]	Tissue concentration	2g Cefazolin	Synovial fluid: 391.3μg/ml Fat Concentration: 247.9μg/g	No	2g Cefazolin	Synovial fluid: 17.6μg/ml Fat Concentration: 11.4μg/g	No
Klasan et al. 2021 [23]	PJI rate	500mg Vancomycin	PJI: 0.3%	AKI 3.0%	3 × 1g Cefazolin	PJI: 0	AKI 5.0%
Park et al. 2021 [22]	PJI rate	500mg Vancomycin	PJI: 0.22%	No	15mg/kg Vancomycin	PJI: 1.4%	No
Parkinson et al. 2021 [19]	PJI rate	1g Cefazolin or 500mg Vancomycin	PJI: 0.1%	No	2g Cefazolin	PJI: 1.4%	No
Harper et al. 2020 [20]	PJI rate	500mg Vancomycin	PJI of Primary TKA: 0 PJI of Revision TKA: 5.3%	No	15mg/kg Vancomycin	PJI of Primary TKA: 0 PJI of Revision TKA: 3.4%	No
Lachiewicz et al. 2023 [21]	PJI rate	500mg Vancomycin	PJI of Revision TKA: 15%	No	No	N/A	N/A
Brozovich et al. 2022 [28]	Pain score and PROM	10mg Morphine	Pain VAS significantly lower than control group; KOOS JR score: 43.9	2 PE	No	N/A	N/A
		0 Morphine	KOOS JR score: 44.5				
		Aged-based doses of Morphine and Ketorolac	Pain VAS: 2.0				

N/A not available; *PJI* prosthetic joint infection; *DVT* deep venous thrombosis; *PE* pulmonary embolism; *AKI* acute kidney injury; *VAS* visual analogue scale; *KOOS JR* Knee Injury and Osteoarthritis Outcome Score for Joint Replacement

Table 3 Risk of Bias in Included Studies

RCT Studies	Cochrane risk of bias tool						
	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Young et al. 2013 [5]	Low	Low	High	Unclear	Low	Low	Unclear
Young et al. 2014 [18]	Low	Low	Low	Low	Low	Low	Unclear
Chin et al. 2018 [14]	Low	Low	High	Unclear	Low	Low	Unclear
Young et al. 2018 [17]	Low	Low	Low	Low	Low	Low	Low
Spangehl et al. 2018	Unclear	Unclear	High	Unclear	Low	Low	Unclear
Zhang et al. 2023 [16]	Low	Low	High	Unclear	Low	Low	Unclear
Brozovich et al. 2022 [28]	Low	Low	Low	Low	Low	Low	Unclear

Non-RCT studies	Risk of Bias in Non-Randomised Studies of Intervention							
	Confounding	Selection of Participants	Classification of Interventions	Deviations from Intended Interventions	Missing Data	Measurements of Outcomes	Selection of Reported Results	Overall bias
Klasan et al. 2021 [23]	Low	Moderate	Low	Low	Low	Low	Low	Low
Park et al. 2021 [22]	Low	Moderate	Low	Low	Low	Low	Low	Low
Parkinson et al. 2021 [19]	Low	Moderate	Moderate	Low	Low	Low	Low	Low
Harper et al. 2020 [20]	Low	Low	Low	Low	Low	Low	Low	Low
Lachiewicz et al. 2023 [21]	N/A	Low	Low	Low	Low	Low	Low	Low

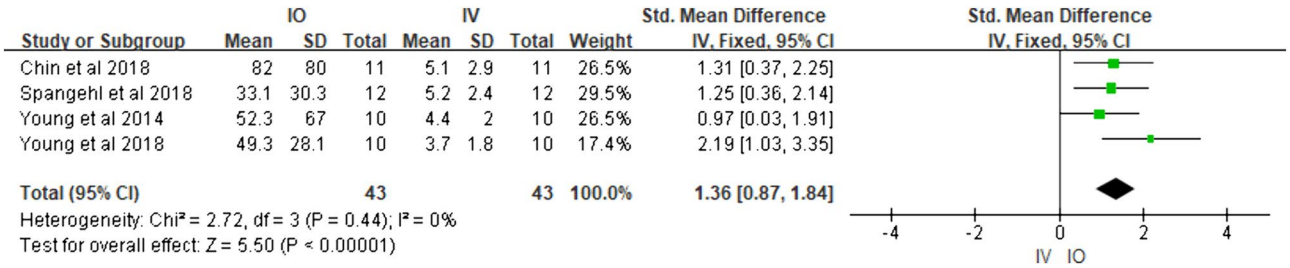

Fig. 2 Vancomycin concentration in periarticular fat tissue. *IO* intraosseous infusion; *IV* intravenous

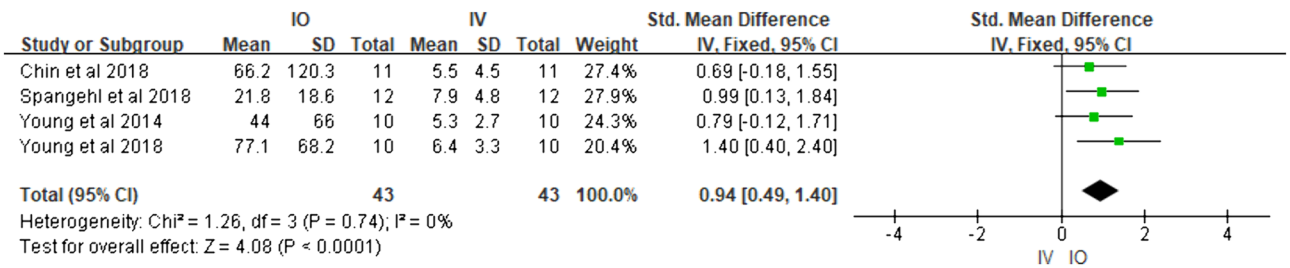

Fig. 3 Vancomycin concentration in bone tissue. *IO* intraosseous infusion; *IV* intravenous

vancomycin. Among them, 5 studies reported the incidence of PJI in primary TKA [14, 19, 20, 22, 23], and 2 studies reported the incidence of PJI in revision TKA [20, 21]. Since both groups had a PJI incidence of 0 in the study by Chin et al. [14], it was not included in the meta-analysis. Previous studies have shown that the incidence of PJI after revision TKA is approximately 9% [24], which is much higher than in primary TKA. Therefore, it is not appropriate to combine primary and revision TKA for analysis. Harper et al. [20] reported the incidence of PJI separately for primary and revision TKA. However, when considering only primary TKA, both groups had a PJI incidence of 0, so this study was also not included in the calculation of OR. The final meta-analysis results showed that compared to IV injection of 1 g vancomycin, IO 500 mg vancomycin was more effective in reducing the incidence of postoperative PJI in primary TKA (OR: 0.19; 95% CI: 0.06–0.59; $P < 0.001$; $I^2 = 36\%$, Fig. 4).

Complications

When discussing the complications of IORA, it can be divided into two aspects: (1) complications related to the IORA technique itself, and (2) complications associated with the drugs administered via IORA. Potential complications of IORA generally include extravasation and compartment syndrome due to improper needle placement, needle bleeding, infection, fat embolism, and neurovascular injury [25–27]. In the studies on IORA in TKA currently available, no cases of injection site bleeding, extravasation, or compartment syndrome were observed. Young et al. [17] reported one case of peroneal nerve injury in the IORA group of their study on revision TKA, with the patient experiencing postoperative foot drop. However, the authors postulated that the foot drop might be related to patient obesity and surgical difficulty, rather than being directly associated with IORA. All 12 studies reported postoperative complications [5, 14–23, 28], and 9 studies found no postoperative complications related to the administration of antibiotics via IORA [5, 15–22]. Regarding IORA-related complications, two studies reported a total of three cases of postoperative pulmonary embolism (PE) [14, 28]. However, as both groups in the study by Brozovich et al. [28]. received drug administration via IORA, a pooled analysis could not be performed.

In studies on preoperative prophylactic IORA of cefazolin in TKA, no drug-related complications were reported [5, 16]. Red man syndrome, acute kidney injury, and neutropenia are commonly recognized complications of vancomycin [29, 30]. In the study by Lachiewicz et al. [21], one patient experienced facial flushing in the postoperative recovery room, which resolved spontaneously without treatment. The authors did not consider it a typical systemic "red man syndrome," and thus, it was not included in the statistical analysis of vancomycin complications. Two studies reported postoperative vancomycin-related complications [18, 23]. Although the incidence of complications in the IO group was lower than in the IV group in both studies, the current meta-analysis results do not support a significant reduction in vancomycin complications with IO administration compared to traditional IV administration (OR: 0.54; 95% CI: 0.25–1.19; $P = 0.44$; $I^2 = 0\%$, Fig. 5).

Discussion

Since its first use in TKA in 2013, several studies have reported that antibiotic administration via IORA significantly increases local drug concentration without a significant increase in systemic complications. However, there is a lack of relevant meta-analyses regarding this topic. Additionally, there is ongoing controversy regarding the prophylactic use of IORA antibiotics to prevent PJI following TKA. In this meta-analysis, we aimed to address these issues. Our findings demonstrate that compared to traditional IV administration, IO vancomycin significantly increases drug concentration in periarticular fat and bone tissue, reduces the incidence of PJI after primary TKA, and does not significantly increase systemic complications.

With advancements in implant design and biomechanical research, infection has emerged as a major cause of primary TKA failure, surpassing aseptic loosening in international studies [31, 32]. The majority of early postoperative infections originate from contamination at the surgical

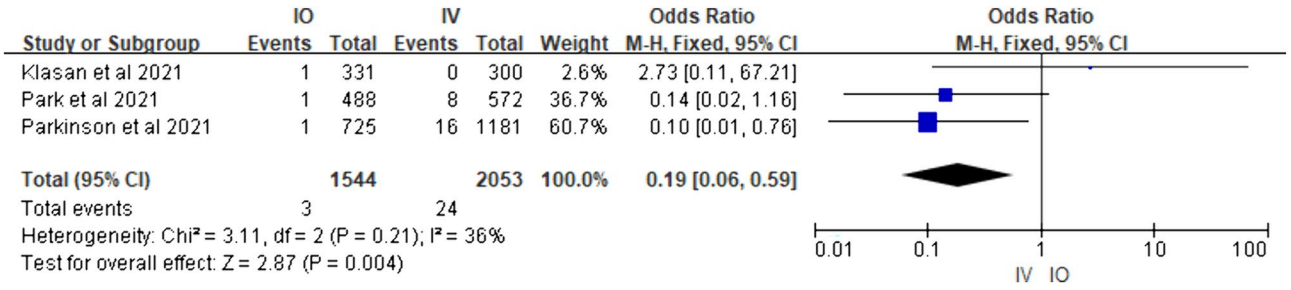

Fig. 4 Prosthetic joint infection rate of primary total knee arthroplasty. *IO* intraosseous infusion; *IV* intravenous

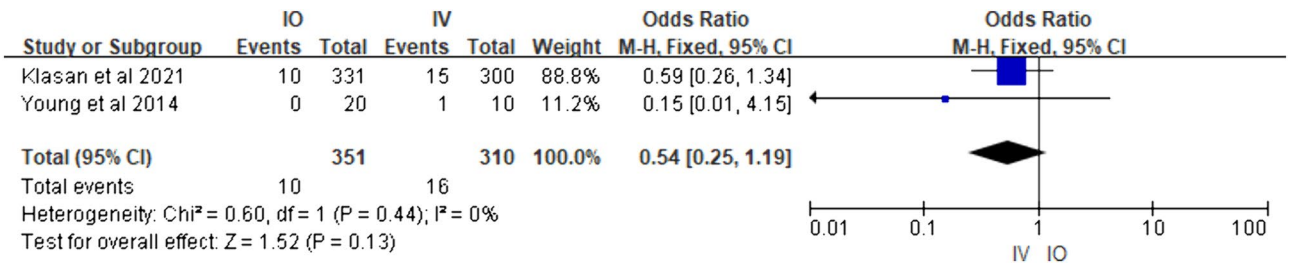

Fig. 5 Complication of vancomycin. *IO* intraosseous infusion; *IV* intravenous

site [33]. Preoperative prophylactic antibiotic use in total knee arthroplasty has been shown to effectively reduce the incidence of PJI [34]. The most common pathogens in PJI are coagulase-negative staphylococci (CoNS) and Staphylococcus aureus (S.A) [35]. Cephalosporins are the most commonly used prophylactic antibiotics in TKA and have demonstrated good effectiveness in clinical practice. However, with increasing antibiotic resistance, the incidence of PJI caused by methicillin-resistant Staphylococcus aureus (MRSA) or drug-resistant CoNS is rising [36]. The tissue concentration of antibiotics must be equal to or greater than the minimum inhibitory concentration (MIC) to achieve effective antibiotic prophylaxis. It has been reported that the resistance of CoNS to cephalothin can increase its MIC90 by approximately 100-fold [37], making it difficult to achieve preventive effects with IV systemic administration. Young et al. [5] first applied IORA antibiotics in TKA and compared the differences in drug concentration in bone and fat tissues between the IORA and IV administration groups in TKA using a RCT. They reported that IORA achieved approximately 10 times higher antibiotic tissue concentration, surpassing the previously reported MIC90 for CoNS and cephalothin [37]. Zhang et al. [16] also supported this conclusion. However, there is currently no research further addressing whether IORA administration of cephalothin can reduce the incidence of PJI after TKA.

Currently, 60–90% of CoNS isolates in joint arthroplasty are resistant to cephalosporins [33, 35], and 33% to 56% of Staphylococcus aureus isolates are resistant to methicillin [4, 38]. However, CoNS and MRSA remain sensitive to vancomycin [35], leading some researchers to propose its use as a prophylactic antibiotic in TKA [18, 39]. However, rapid infusion of vancomycin can lead to complications such as red man syndrome, requiring a maximum infusion rate of 1 g/h [39]. Furthermore, due to the potential nephrotoxicity of vancomycin [40] and the potential for increased bacterial resistance, the routine use of IV vancomycin as prophylaxis in TKA is not common [39]. Young et al. [18] first used IORA to administer vancomycin as preoperative prophylaxis in TKA. They compared the differences in drug concentrations in bone and fat tissues between IORA 250 mg vancomycin, IORA 500 mg vancomycin, and the conventional regimen (IV administration of 1 g vancomycin) and found that at 80 min after the start of surgery, the tissue concentrations of vancomycin in both IORA groups were significantly higher than in the IV group. Additionally, the tissue concentration of vancomycin in the IORA 500 mg group had the highest ratio of MIC for CoNS (99%), demonstrating that the tissue concentration of low-dose IORA vancomycin was superior to that achieved with traditional systemic administration. Although vancomycin is a time-dependent antibiotic, its long postantibiotic effect (PAE) is similar to concentration-dependent antibiotics in terms of pharmacokinetic/ pharmacodynamic (PK/PD) parameters and effectiveness prediction. An area under the curve (AUC)/MIC ratio of ≥ 400 for vancomycin can rapidly clear bacteria [41]. By using the IORA route, not only the time constraints of traditional administration can be overcome, but higher tissue concentrations can be quickly achieved after the start of surgery, which can improve effectiveness and duration of action by increasing the AUC [14]. Subsequent studies have mostly used a prophylactic antibiotic regimen of IORA 500 mg vancomycin in TKA [14, 15, 17, 19–23]. However, as vancomycin is a narrow-spectrum antibiotic with strong bactericidal activity against gram-positive bacteria, which only accounts for approximately 82% of the pathogens causing PJI after total joint arthroplasty [42]. Some studies have reported an increased incidence of PJI when vancomycin is used alone for preoperative prophylaxis in TKA [43]. Furthermore, the use of antibiotics administered via IORA is still in the research stage, and in most of the current studies, the experimental groups also received cephalosporin antibiotics intravenously [5, 14, 15, 17–23].

It have been shown that although no statistical or clinical differences were found, IORA increases tourniquet time by approximately 2 min [20, 22], which may have negative implications, including increased postoperative pain, increased inflammatory response, and decreased quadriceps strength [44]. Therefore, many surgeons tend to minimize the use of tourniquets during the surgical procedure [45]. To investigate whether short-duration tourniquet inflation would affect tissue concentrations of IORA antibiotics in TKA,

Spangehl et al. [15] released the tourniquet after only 10 min of inflation following prophylactic IORA 500 mg vancomycin, demonstrating that brief tourniquet use achieved tissue drug concentrations similar to those achieved with conventional tourniquet use.

Previous follow-up studies and the present study have confirmed that the use of IORA antibiotics prior to primary TKA is non-inferior to conventional systemic IV antibiotic regimens in preventing postoperative PJI [19, 20, 22, 23]. However, the effectiveness of IORA antibiotics in high-risk patients for infection remains controversial. Although Chin et al. [14] demonstrated that local tissue concentrations were 5–9 times higher in obese patients (BMI > 35 kg/m^2) receiving IORA vancomycin compared to the IV group, Parkinson et al. [19] found in subgroup analysis that IORA vancomycin did not reduce the incidence of PJI in high-risk populations such as obese (BMI > 35 kg/m^2), renal failure, and diabetes. However, due to the small size of the study cohorts in high-risk populations, clinical evidence is currently insufficient.

The incidence of PJI is higher in revision TKA, and the treatment of PJI after revision TKA is more challenging due to the concurrent use of extended stems, metal inserts, and metal bone struts [46]. This highlights the greater significance of prophylactic antibiotic use in revision TKA. Harper et al. [20] reported a retrospective cohort study of 48 cases of revision TKA, comparing prophylactic IORA vancomycin with conventional regimens, and found no statistically significant difference in the incidence of postoperative PJI. Lachiewicz et al. [21] prospectively followed 20 patients undergoing revision TKA for non-infectious reasons for 90 days, and three cases of PJI occurred within 90 days postoperatively, showing no significant improvement in the incidence of PJI compared to the previously reported rates in the same treatment group. Although Young et al. [17] also achieved significantly increased local drug concentrations using IORA antibiotics in revision TKA, their effectiveness in reducing postoperative PJI incidence appears to be limited. To our knowledge, there are currently no prospective, RCTs on the use of IORA antibiotics in aseptic revision TKA. It should be emphasized that the formation of a biofilm by pathogens on the surface of the prosthesis is a significant factor in PJI [47], and bacteria within the biofilm may have MICs that are 1000 times higher than before biofilm formation [48]. Systemic antibiotic administration alone cannot achieve effective local concentrations, and traditional local administration methods are difficult to maintain effective concentrations for a long time. The colonization of pathogens on the surface of the prosthesis may be an important factor affecting the effectiveness of IORA antibiotics. Future research may be needed to evaluate the application value of IORA administration techniques in TKA through studies targeting pathogenic bacteria on the surface of the prosthesis.

No complications at the injection site, fluid extravasation, or compartment syndrome were observed in studies using IORA in TKA. Although animal studies have shown histological evidence of pulmonary microembolism following IO [49], no cases of fat embolism after IORA administration have been reported in humans. Although three cases of postoperative PE were reported in the IORA group in the current studies, the limited number of cases necessitates further large-scale trials to determine whether IORA increases the incidence of PE. This meta-analysis didn't find a statistically significant difference in complications between IORA and IV vancomycin. However, in the two studies reporting vancomycin complications, the incidence of complications in the IORA group was lower than in the IV group. IORA may have advantages in reducing systemic drug-related complications.

This meta-analysis has several limitations. Firstly, although we included a total of 12 studies in our analysis, there were limited studies reporting the incidence of PJI and complications, and they were not RCTs. We hope that future research can provide further support for our conclusions through more large-scale retrospective studies or RCTs. Secondly, due to the potential for promoting microbial resistance with routine use of vancomycin, some scholars have suggested that it is preferable to limit the use of IORA vancomycin for infection prophylaxis to high-risk patients for PJI. Cephalosporins are the main prophylactic drugs used prior to TKA, but currently, only two studies have used IORA cefazolin, and there have been no reports on whether it can reduce the incidence of PJI after TKA. Thirdly, some studies included in this meta-analysis did not report the minimum follow-up and among the other studies, the minimum follow-up were less than 12 months [50]. Therefore, this study cannot answer the effect of IORA prophylactic antibiotics on late infections. Fourthly, our study was unable to answer whether prophylactic IORA antibiotics have an advantage in reducing the incidence of PJI in high-risk populations such as obese, renal failure, diabetic, or revision TKA patients. We intended to perform subgroup analysis based on primary/revision TKA, but one study reporting the incidence of PJI in revision TKA was a single-arm retrospective cohort study [21], making it impossible to conduct subgroup analysis for the incidence of PJI in revision TKA. Therefore, in this study, we only analyzed the incidence of PJI in primary TKA.·Our findings may only be applicable to patients undergoing routine primary TKA, and more research is needed in high-risk PJI populations. Fifthly, due to the limited number of studies reporting complications, we included both RCTs and non-RCTs in our statistical analysis, which may introduce heterogeneity among the studies and affect the conclusions. However, the statistical results did not show significant heterogeneity. Lastly, due to

the small number of studies included in this study, we have not conducted a publication bias analysis.

Conclusions

This study demonstrates that preoperative prophylactic antibiotics administered via IORA in TKA significantly increase local drug concentration without significantly increasing systemic complications. IO vancomycin is effective in reducing the incidence of PJI in routine primary TKA. However, its effectiveness in high-risk populations for PJI, such as obese individuals, those with diabetes, renal insufficiency, as well as in revision TKA, remains controversial. Future research should include larger RCTs and longer follow-up periods to further clarify the value and safety of antibiotic administration via IORA.

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Declarations

Conflict of interest All authors complete the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest.

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