Synovial vancomycin and meropenem concentrations in periprosthetic joint infection treated by single-stage revision combined with intra-articular infusion

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Cite this article:
Bone Joint Res 2024;13(10):
535–545.

DOI: 10.1302/2046-3758.
1310.BJR-2024-0024.R2

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Aims

We aimed to determine the concentrations of synovial vancomycin and meropenem in patients treated by single-stage revision combined with intra-articular infusion following periprosthetic joint infection (PJI), thereby validating this drug delivery approach.

Methods

We included 14 patients with PJI as noted in their medical records between November 2021 and August 2022, comprising eight hip and seven knee joint infections, with one patient experiencing bilateral knee infections. The patients underwent single-stage revision surgery, followed by intra-articular infusion of vancomycin and meropenem (50,000 µg/ml). Synovial fluid samples were collected to assess antibiotic concentrations using high-performance liquid chromatography.

Results

The peak concentrations of vancomycin and meropenem in the joint cavity were observed at one hour post-injection, with mean values of 14,933.9 µg/ml (SD 10,176.3) and 5,819.1 µg/ml (SD 6,029.8), respectively. The trough concentrations at 24 hours were 5,495.0 µg/ml (SD 2,360.5) for vancomycin and 186.4 µg/ml (SD 254.3) for meropenem. The half-life of vancomycin was 6 hours, while that of meropenem ranged between 2 and 3.5 hours. No significant adverse events related to the antibiotic administration were observed.

Conclusion

This method can achieve sustained high antibiotic concentrations within the joint space, exceeding the reported minimum biofilm eradication concentration. Our study highlights the remarkable effectiveness of intra-articular antibiotic infusion in delivering high intra-articular concentrations of antibiotics. The method provided sustained high antibiotic concentrations within the joint cavity, and no severe side-effects were observed. These findings offer evidence to improve clinical treatment strategies. However, further validation is required through studies with larger sample sizes and higher levels of evidence.

Article focus

- To investigate the pharmacokinetic trends of vancomycin and meropenem in synovial fluid following single-stage revision arthroplasty, providing a foundation for optimizing clinical treatment strategies.

Key messages

- This study initially explored the pharmacokinetics of vancomycin and meropenem within the joint cavity environment, demonstrating that the trough concentrations of both drugs can be sustained above the pathogen's minimum biofilm eradication concentration over an extended period.

- Based on the scope of this study, no significant toxic side-effects were found after the intravenous combined with local high-concentration continuous use of antibiotics.

Strengths and limitations

- This is the first study to provide a comprehensive and continuous analysis of antibiotic concentrations in the joint following single-stage revision for periprosthetic joint infection.
- Due to a uniform local antibiotic regimen and varied systemic treatments among patients, this study could not analyze how serum pharmacokinetics affect joint drug concentrations.
- The study involved a retrospective analysis on prospective data, which limits the level of evidence. Further exploration is warranted through more extensive randomized controlled trials with larger sample sizes to validate and expand upon our findings.

Introduction

Periprosthetic joint infection (PJI) is a devastating complication following joint arthroplasty surgery, often requiring revision surgery. The incidence of PJI varies between 1% and 2% for primary hip and knee arthroplasties,[1] and the reinfection rate after revision in some circumstances can range from 5.8% to 16.2%.[2]

A factor contributing to the difficulty of treating PJI and the high recurrence rates is the formation of bacterial biofilms on the prosthetic surface.[3] Biofilms are complex microbial communities embedded within a self-produced extracellular matrix, protecting the bacteria from the host immune systems and antibiotics.[4] Conventional systemic antibiotic treatments often fail to achieve sufficient concentrations to eradicate the biofilm, leading to persistent infections and treatment failures. Once biofilms are formed, high concentrations of antibiotics are required for effective treatment, with the minimum biofilm eradication concentration (MBEC) typically 100 to 1,000 times greater than the minimum inhibitory concentration (MIC) for planktonic bacteria.[5] Therefore, continuous local antibiotic administration following single-stage revision is important to address the challenges posed by bacterial biofilms.[6-8]

Single-stage revision surgery is an appealing alternative treatment method, boasting cure rates comparable to or surpassing those of two-stage revision.[9-11] Furthermore, integrating the intra-articular administration of antibiotics, such as vancomycin, meropenem, imipenem, tigecycline, and voriconazole, is effective.[12-17] However, dosing and frequency adjustments are primarily empirical and lack a solid theoretical basis. We therefore aimed to measure and analyze antibiotic concentrations in the joint cavity after single-stage revision, providing preliminary insights into the pharmacokinetics within the joint environment and offering a basis to adjust clinical treatment plans in the future.

Methods

Design

We retrospectively reviewed data collected from medical records between November 2021 and August 2022, and included patients diagnosed with PJI according to the Musculoskeletal Infection Society (MSIS) criteria,[18] who underwent a single-stage revision, receiving simultaneous intra-articular injections of vancomycin (Vianex, Greece) and meropenem (Sumitomo Pharma, Japan). We excluded patients who did not have synovial fluid collected according to the predetermined protocol, or those who had their antibiotic treatment plan changed based on pathogen culture results and drug sensitivity findings (Figure 1).

Patient demographics and baseline characteristics

Between November 2021 and August 2022, 14 patients with 15 PJIs were treated. The distribution of knee and hip joint infections was nearly equal within this group. The mean age was 63.3 years (40.0 to 78.0), and the mean BMI was 25.3 kg/m^2 (19.0 to 39.0). The aetiological characteristics of the 14 patients in this study revealed a predominance of gram-positive bacteria, particularly staphylococcal infections (Table I).

Surgical procedure

All surgeries were performed by a senior surgeon (LC) specializing in revision surgery and infection management, focusing on single-stage revisions. Targeted antibiotics were determined by preoperative aspiration culture and sensitivity tests, administered intravenously 30 minutes before skin incision.

The surgery had two phases. The first phase involved aggressive debridement, removing necrotic tissue, bone sequestra, and inflammatory synovium, followed by component and cement debris elimination. The site was irrigated with saline, ultrasound pulses, and hydrogen peroxide, and soaked in betadine before sterilization and redraping.

The surgical team then rescrubbed and changed instruments for the second phase. In hip PJI cases, 0.5 g vancomycin or meropenem was applied to the femoral canal and acetabulum base; in knee PJI cases, it was applied to the distal femoral and proximal tibial canal. A new prosthesis was implanted. Revision hips used cementless implants, while knees used gentamicin-loaded cement. An additional 0.5 g vancomycin powder was added to the joint cavity before closing the deep fascia. The incision was sealed, with a suction drain placed distally and a three-branch catheter positioned proximally for postoperative intra-articular antibiotic infusion (Figure 2).

Sonication fluid was incubated in blood culture bottles and cultured using the BACT/ALERT 3D system (bioMérieux, France), alongside synovial fluid for comparison. Samples were sent to a microbiology lab for culture, sensitivity tests, and histological evaluation.

Postoperative antibiotic protocol

The postoperative antibiotic regimen was determined based on culture results, drug sensitivity tests, and patient condition, in collaboration with the clinical pharmacy team.[19] Prior to receiving results, patients typically received intravenous vancomycin 1,000 mg every 12 hours, combined with 500 mg vancomycin and 500 mg meropenem which was dissolved in 10 ml saline and injected into the joint via a three-branch catheter every 24 hours. Drainage tubes were unclamped and functional six hours after each local antibiotic administration. Our criteria for the removal of the drainage tube was a daily drainage volume of less than 100 ml. After drainage tube

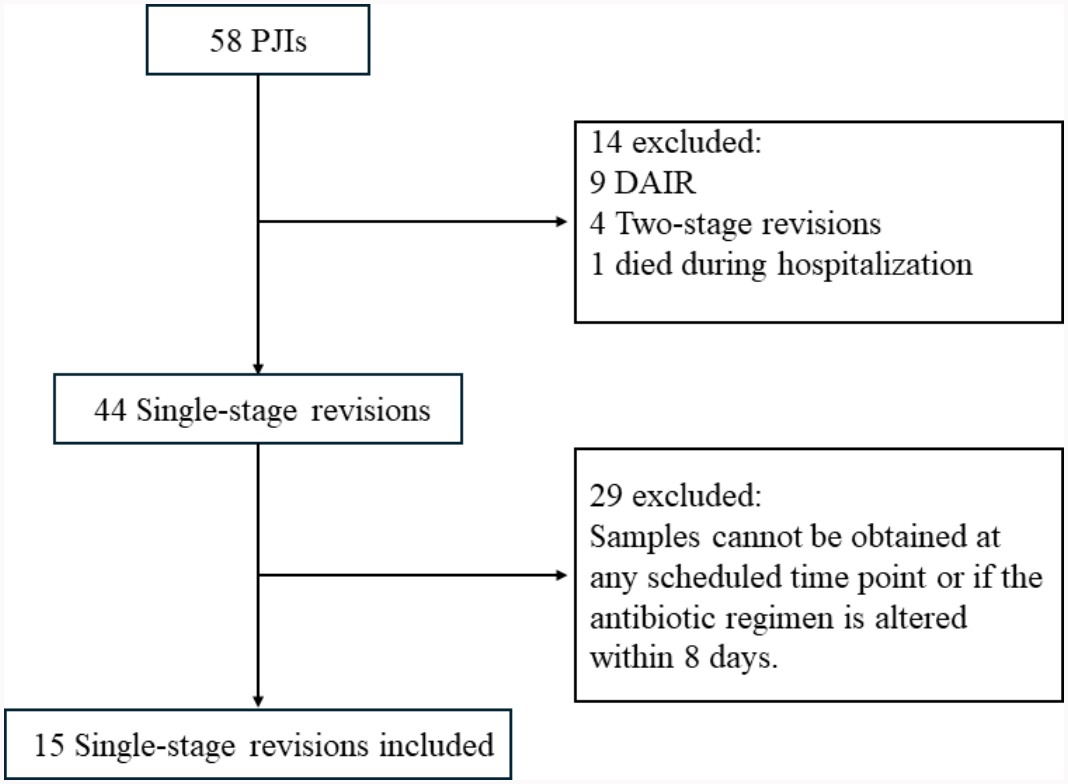

Fig. 1
Flow diagram showing the constitution of the cohort. DAIR, debridement, antibiotics, and implant retention; PJI, periprosthetic joint infection.

Table I. Demographic data for 14 periprosthetic joint infection patients (15 joints).

ID	Sex	Age, yrs	Operation site	BMI, kg/m^2	Comorbidities	ASA grade	Number of prior surgeries	Pathogens	Antibiotic regimens	
									IV	IA
1	F	68	Hip	23	TB, ARR	III	5	*E. coli, S. aureus*	MEM 7d	VAN + MEM 8d
2	F	68	Knee	24	HT, DM	III	2	*Bacillus cereus, Bacillus subtilis*	VAN 7d	VAN + MEM 8d
3	F	64	Hip	24	HT, DM, CHD, RA	III	3	*S. epidermidis*, MRSE	VAN 7d	VAN + MEM 8d
4	M	68	Knee	27	None	II	2	MRSE	VAN 5d	VAN + MEM 8d
5	M	74	Knee	23	AM, ARR	III	2	MRSA	VAN 8d	VAN + MEM 8d
6	M	40	Hip	26	None	II	6	MRSA	VAN 8d	VAN + MEM 8d
7	F	59	Knee	19	RA	II	3	*Bacillus firmus*	VAN 8d	VAN + MEM 8d
8	F	61	Hip	39	HT, RA	III	2	*S. hominis*	VAN 8d	VAN + MEM 8d
9	M	63	Hip	26	PC	III	2	*Streptococcus mitis*	VAN + MEM 7d	VAN + MEM 8d
10	M	51	Hip	30	HT, RF	III	4	*S. aureus*	VAN 5d	VAN + MEM 8d
11	F	60	Knee	20	None	III	2	MRSE	VAN 7d	VAN + MEM 8d
12	F	78	Hip	19	MT, AM	III	3	*E. coli, S. aureus*	VAN + MEM 8d	VAN + MEM 8d
13	M	77	Hip	22	ARR, HT, CKD	III	4	MRSE	VAN + MEM 6d	VAN + MEM 8d
14	F	56	Knee	33	None	II	2	MRSE, *S. lugdunensis*	VAN 8d	VAN + MEM 8d

AM, anaemia; ARR, arrhythmia; ASA, American Society of Anesthesiologists; CHD, coronary arterial disease; CKD, chronic kidney disease; DM, diabetes mellitus; *E. coli*, *Escherichia coli*; HT, hypertension; IA, intra-articular; IV, intravenous; MEM, meropenem; MRSA, methicillin-resistant *S. aureus*; MRSE, methicillin-resistant *S. epidermis*; MT, malignant tumour; PC, pericoronitis; RA, rheumatoid arthritis; RF, respiratory failure; *S. aureus*, *Staphylococcus aureus*; *S. epidermis*, *Staphylococcus epidermis*; *S. hominis*, *Staphylococcus hominis*; *S. lugdunensis*, *Staphylococcus lugdunensis*; TB, pulmonary tuberculosis; VAN, vancomycin.

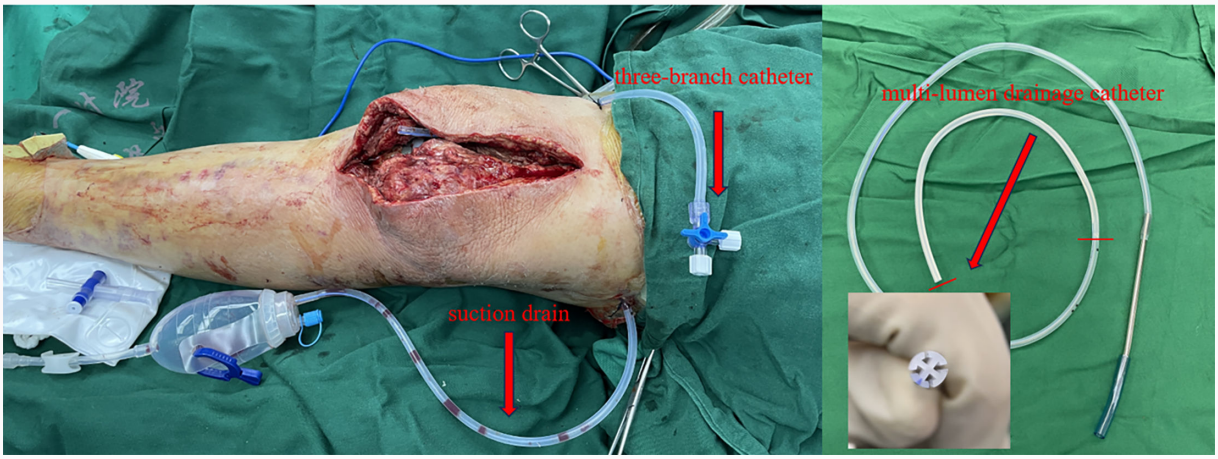

Fig. 2
Intra-articular suction drain and three-branch catheter were placed into the knee joint. The same approach was also applied to the hip joint.

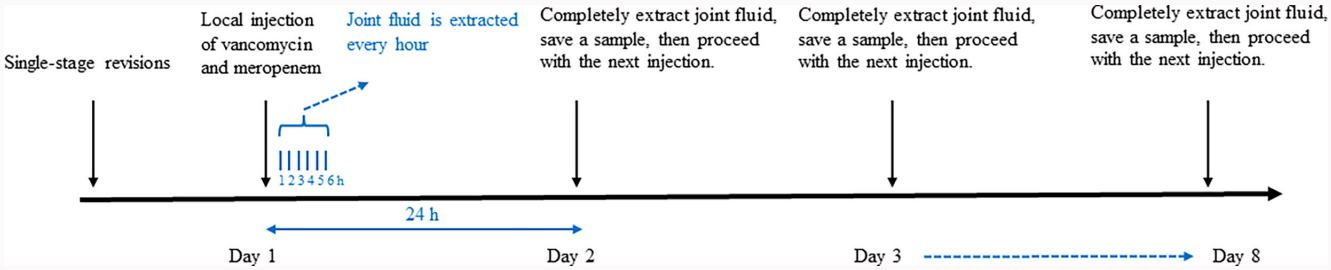

Fig. 3
Flow diagram showing the timeline for antibiotic regimen and sample collection.

removal, joint fluid was thoroughly aspirated through the three-branch catheter before each injection.

Upon receiving pathogen culture results, the antibiotic treatment plan was adjusted accordingly. During surgery, at least ten samples were analyzed using ultrasonic technology, with two to three groups indicating the same bacteria considered monobacterial infection. For gram-positive infections, 1,000 mg vancomycin was administered intravenously every 12 hours, and 500 mg locally in the joint cavity daily. For gram-negative infections, 1,000 mg meropenem was administered intravenously every eight hours, and 500 mg locally once per day. In cases of multiple infections or preoperative sinus tract formation, combined intra-articular medication, typically vancomycin and meropenem, was maintained. For special pathogens, the antibiotic regimen was adjusted to use imipenem, tigecycline, voriconazole, or linazolid. The patients included in this study all underwent an eight-day treatment regimen of intra-articular vancomycin and meropenem combination therapy, but it is not the endpoint of the treatment. Antibiotics are typically administered for a duration of two weeks postoperatively, with the cessation timing being determined by a comprehensive consideration of the patient's clinical indicators and symptomatology.

Sample collection and measurement

The study design involved initiating local intra-articular antibiotic injections daily, starting on the first day post-surgery. Synovial fluid samples were collected hourly, one to six hours after the initial injection, and immediately before each subsequent 24-hour injection. Peak concentration was determined by measuring the concentration continuously over a period of six hours, while trough concentration was evaluated directly before the second injection at 24 hours and before each subsequent injection. Samples were collected until the eighth postoperative day. Consecutive six-hour samples on the first day helped investigate the decay trend and half-life of vancomycin and meropenem in the joint cavity. Samples were centrifuged at 4,000 RPM for five minutes, and the supernatant was stored at -80°C. Drug concentrations were measured using high-performance liquid chromatography (HPLC) (Supplementary Material) (Figure 3).

Assessment of relevant clinical indicators

Preoperative baseline clinical indicators were ascertained for all patients through haematological and synovial fluid assays. Postoperative haematological evaluations were mandated daily for an uninterrupted period of three days, with the provision for extending the interval to every 48 to 72 hours in cases of clinical equipoise. Daily biochemical analysis of synovial fluid was compulsory. In this study, a comparative analysis of the final clinical indices on day 8 post-treatment was conducted against the preoperative baselines. All measurements were conducted by the hospital's laboratory department without the implementation of blinding.

Statistical analysis

Data are presented as means and SD, unless otherwise specified. Sample number (n) represents the number of independent patients in each group. Correlations were described using Pearson correlation coefficient. For comparisons, a one- or two-sided independent-samples *t*-test was used to detect differences in groups when data met the homogeneity of variance; otherwise, an unequal variance *t*-test was used. But in cases where data failed normality assumptions, Wilcoxon signed-rank test were utilized instead. A p-value of < 0.05 was considered statistically significant.

Results

Synovial concentrations of vancomycin and meropenem

The total peak concentration of vancomycin within the joint cavity was 14,933.9 µg/ml (SD 10,176.3), which decreased to 7,043.7 µg/ml (SD 2,969.1) by the sixth hour. The mean trough concentration from days 2 to 8 was 5,495.0 µg/ml (SD 2,360.5). For meropenem, the total peak concentration was 5,819.1 µg/ml (SD 6,029.8), and it decreased to 411.2 µg/ml (SD 639.5) by the sixth hour. The mean trough concentration from days 2 to 8 was 186.4 µg/ml (SD 254.3).

In the knee joint, the peak concentration of vancomycin was 14,288.9 ml (SD 4,764.8), which declined to 7,319.7 µg/ml (SD 2,647.9) by the sixth hour. The mean trough concentration from days 2 to 8 was 6,724.8 µg/ml (SD 2,144.3). Meropenem concentrations in the knee joint decreased from 4,374.3 µg/ml (SD 4,393.2) at one hour to 403.1 µg/ml (SD 774.8) by the sixth hour. The mean trough concentration was 199.4 µg/ml (SD 259.8).

In the hip joint, the peak concentration of vancomycin was 16,273.8 µg/ml (SD 10,795.7), which decreased to 6,802.3 µg/ml (SD 3,204.5) by the sixth hour. The mean trough concentration was 4,418.9 µg/ml (SD 1,985.7). Meropenem concentrations decreased from 7,083.3 µg/ml (SD 6,918.1) at one hour to 418.3 µg/ml (SD 491.3) by the sixth hour. The mean trough concentration from days 2 to 8 was 175.0 µg/ml (SD 248.8). There was no significant difference in the concentrations of the two drugs in the hip and knee joints.

Based on the observed trends at different timepoints, the estimated half-life of vancomycin within the joint cavity is approximately six hours, while that of meropenem ranges between two and 3.5 hours (Figure 4). Perioperative factors such as drainage volume, intraoperative bleeding, and serum albumin levels may impact the antibiotic concentrations in the joint space, but no specific patterns were evident (Figure 5).

Treatment efficacy and safety indicators

We observed a significant post-treatment decrease in drainage volume across the board, underscored by robust statistical significance ($p < 0.001$ total; $p < 0.001$ hip; $p = 0.013$ knee, Wilcoxon signed-rank test). A considerable reduction in synovial fluid leucocyte count was noted ($p < 0.001$ total, Wilcoxon signed-rank test), with a trend towards significance in the hip ($p < 0.001$, Wilcoxon signed-rank test) and clear importance in the knee ($p = 0.008$, Wilcoxon signed-rank test). A notable decline in the proportion of multinucleated cells, commonly linked to inflammatory and infectious processes, was statistically validated for all examined sites ($p < 0.001$ total; $p = 0.009$ hip; $p = 0.002$ knee, independent-samples *t*-test). ESR levels exhibited a marked decrease post-intervention ($p < 0.001$ for all sites, independent-samples *t*-test), aligning with the trend seen in CRP concentrations, which also significantly diminished ($p < 0.001$ total; $p = 0.002$ hip; $p = 0.016$ knee, independent-samples *t*-test). Renal function markers, blood urea nitrogen (BUN), and creatinine remained stable post-treatment, reinforcing the renal safety of the therapeutic approach (Table II).

In the study, two patients experienced a recurrence of the infection within one year after the surgery: one underwent a second single-stage revision surgery, while the other patient underwent a DAIR procedure. Neither had recurrent infections at the latest follow-up.

Discussion

The treatment of PJI has seen increasing use of local antibiotic administration within joints across various medical centres.[20-28] Utilizing intravenous and local antibiotics in tandem improves clinical outcomes for patients, allowing for a more targeted and comprehensive treatment and ensuring effective management of the infection.[29] The local administration of antibiotics can shorten the duration of intravenous therapy, thereby avoiding systemic toxic side-effects. Additionally, it provides a sustained high concentration of antibiotics within the joint. In our recent treatments, we have attempted to reduce the duration of intravenous antibiotic use, such as administering intravenous antibiotics for only 48 hours postoperatively in patients without systemic infection symptoms.

By adopting a comprehensive treatment system incorporating single-stage revision surgery and local intra-articular antibiotic injections, our centre has achieved favourable outcomes in managing complex cases of PJI. Our approach has proven effective in treating patients with various challenging scenarios, including patients with: a history of multiple failed surgeries; bacterial infections; gram-negative organisms; culture-negative PJI; debridement, antibiotics, and implant retention; and even fungal PJI. For more specific details, please review our previously published literature.[12-17] Although satisfactory therapeutic effects have been achieved, the antibiotic regimen is still largely empirical and needs to be optimized based on further research.

S. epidermidis is the most common pathogen found in PJI. The proportion of MRSE in hip joint infections is higher than in the knee joint (50% and 35%, respectively). MRSA is found in similar percentages. Gram-negative bacteria are present in 5% of hip joint cases and 10.3% of knee joint cases.[30,31] Moreover, the dynamic nature of antibiotic resistance among pathogens poses a challenge in the effective management of infections.[32] Antibiotic regimens must be designed carefully considering the resistance patterns and complexity of these microorganisms.[33]

Vancomycin is an effective antibiotic against gram-positive bacteria, particularly drug-resistant strains such as MRSA and MRSE. It is a glycopeptide and time-dependent antibiotic, with its clinical activity influenced by factors such as tissue distribution, inoculum size, and emerging resistance.[34] Various medical centres have collectively selected vancomycin as their antibiotic for the treatment of gram-positive PJI.[22–27] By contrast, gram-negative bacterial infections are less common in PJI, and aminoglycoside antibiotics, such as gentamicin, tobramycin, or amikacin, are used to treat these

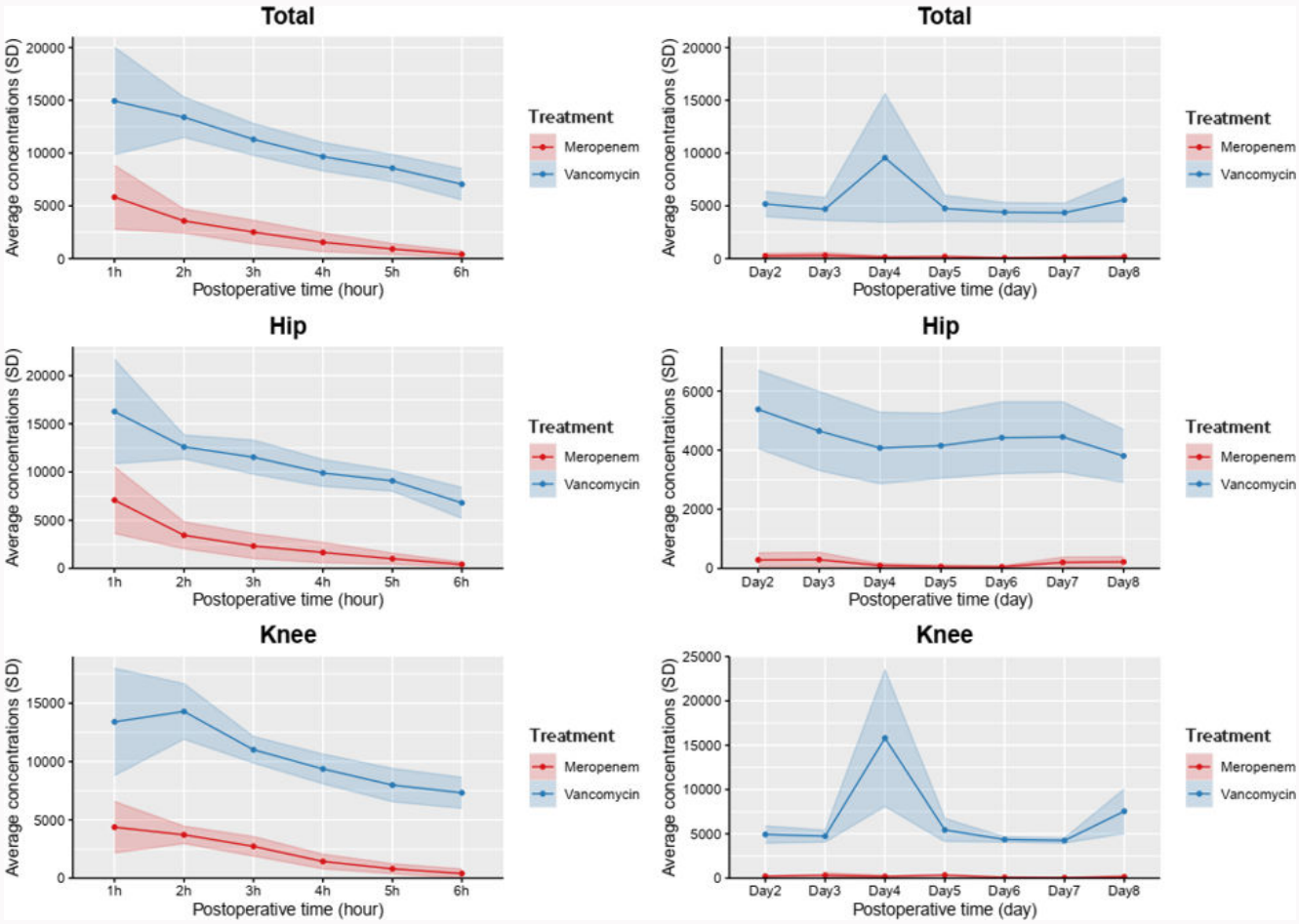

Fig. 4
Intra-articular concentration levels of vancomycin and meropenem.

infections. Additionally, carbapenem antibiotics, particularly meropenem, demonstrate superior efficacy against gram-negative bacteria, especially *E. coli*, compared to imipenem.[35] Meropenem, a broad-spectrum carbapenem antibiotic, has excellent penetration capabilities, allowing it to reach various tissues and biological compartments, including the joint cavity. This characteristic is essential for the drug to effectively target and eliminate bacterial pathogens at the site of infection. However, the stability of meropenem is lower than other antibiotics, resulting in faster degradation and a shorter half-life.[36]

We opt for a postoperative regimen that combines intravenous and local route for antibiotic administration, utilizing vancomycin and meropenem in scenarios where the infectious pathogen is not specifically identified, or under special circumstances. The regimen for intra-articular administration of antibiotics provides broad-spectrum coverage, targeting both gram-positive and gram-negative bacteria, including methicillin-resistant strains. The synergistic effect of vancomycin and meropenem against specific bacterial pathogens enhances their bactericidal activity.[35-37] The peak and trough concentrations of vancomycin in the joint were higher than those of meropenem. Furthermore, meropenem exhibited a faster half-life within the joint cavity, which aligns with the pharmacokinetic behaviour of both drugs in the bloodstream.

The antibiotic susceptibility of gram-positive and gram-negative bacteria surrounding PJIs has been investigated. For meropenem, the ranges of the MIC, minimal bactericidal concentration (MBC), minimal biofilm inhibitory concentration (MBIC), and MBEC against various gram-negative bacteria are 0.03125 µg/ml to 32 µg/ml. Conversely, for vancomycin targeting gram-positive bacteria, these values range from 0.25 µg/ml to 1,216 µg/ml.[38,39] We determined that the mean trough concentrations of meropenem and vancomycin within the joint cavity were 186.4 µg/ml (SD 254.3) and 5,495.0 µg/ml (SD 2,360.5), respectively, which were significantly higher than the MBEC required for the targeted pathogens.

There are several methods available to sustain the levels of antibiotics within the joint cavity. Vancomycin has been administered intravenously to patients after undergoing primary total knee arthroplasty.[40] Spacers are also used as specialized implants composed of bone cement and antibiotics, and are placed in the infected joint to stabilize it and provide continuous local antimicrobial therapy through antibiotic release. Rate reduction after initial burst release is common in antibiotic-loaded cements, and antibiotic concentrations vary significantly across studies.[41-43] In a study utilizing two unique concentrations (1 g of antibiotic/10 g of polymethyl methacrylate (PMMA) and 2 g of antibiotic/10 g of PMMA), vancomycin concentrations reached 4 µg/ml to

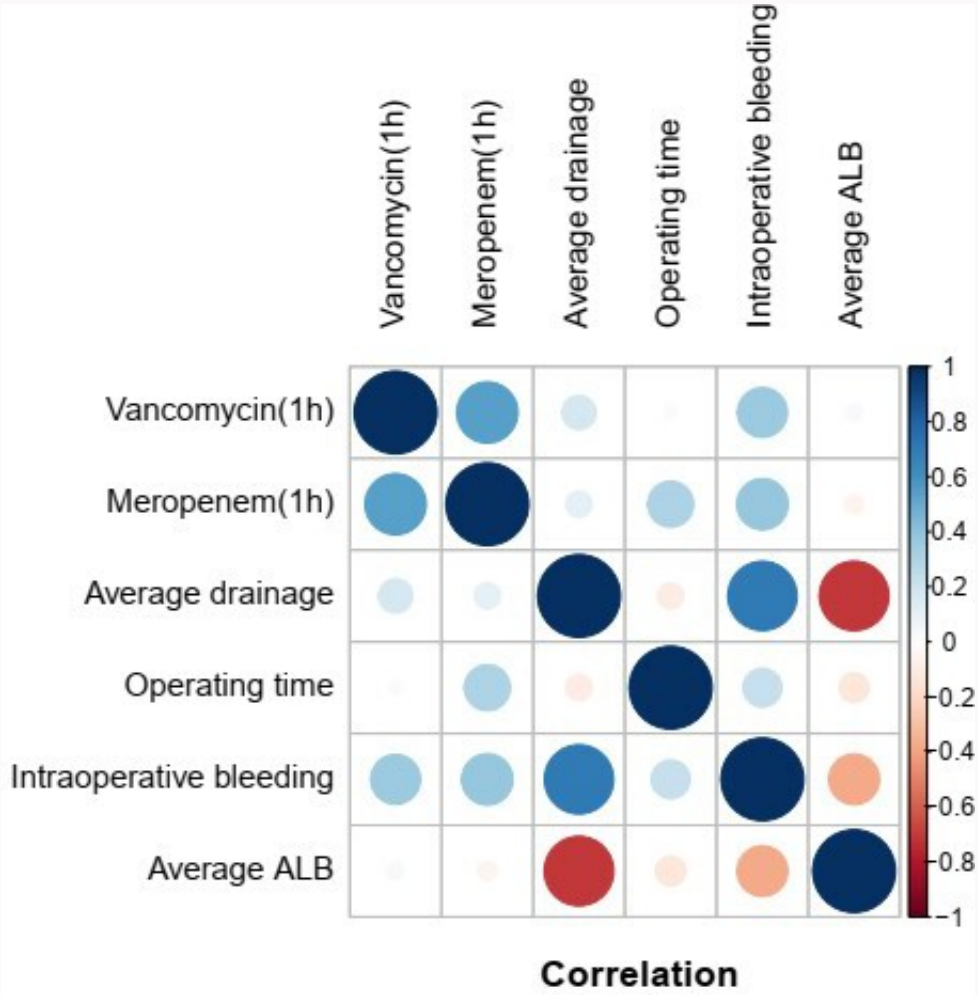

Fig. 5
Correlation analysis of peak drug concentration in the joint cavity. ALB, albumin.

8 μg/ml after one week, while meropenem concentrations ranged from 8 μg/ml to 14 μg/ml and steadily declined over a 30-day period.[44] Calcium sulphate beads are another method for local antibiotic delivery in orthopaedic infections.[45] In an in vitro study, the purpose was to quantify the elution kinetics of six antibiotics with an initial concentration of 1,024 μg/ml. Vancomycin concentration was approximately 1,000 μg/ml at 20 hours and decreased to 1 μg/ml after 600 hours. Meanwhile, meropenem maintained a concentration of 1,000 μg/ml at 20 hours and was reduced to only 0.2 μg/ml after 600 hours.[46] Additionally, intraosseous antibiotic injection is a viable method.[47] However, these methods cannot maintain drug concentrations above the MBEC within the joint cavity, and long-term subtherapeutic treatment may increase the risk of bacterial resistance. Contrastingly, direct intra-articular injection of antibiotics can consistently achieve drug concentrations higher than the MBEC, and the method is simple, allowing for flexible adjustment of the treatment plan.

In PJI, a mature biofilm often forms around the implant. Despite employing diverse debridement techniques during revision surgery, complete pathogen elimination remains a challenge, leaving residual bacteria in the soft-tissues and bones, which contribute to infection recurrence.[48] Therefore, it is vital to maintain drug concentrations within the joint above the MBEC for an extended duration. Furthermore, infections involving implanted devices should give more consideration to the MBEC.[49]

Few studies have investigated the use of intra-articular antibiotics concentrations in PJI. Whiteside et al[50] assessed intra-articular vancomycin concentrations in 11 patients, and the mean synovial peak level was 9,242 μg/ml following injection. The trough level had a mean of 377 μg/ml, and the elimination half-life of intra-articular vancomycin among individual patients ranged from 1.61 to 4.70 hours, with a mean of 3.22 hours. These values are consistent with other studies.[23] Furthermore, vancomycin 0.5 g once daily administered intra-articularly and vancomycin 1 g every 12 hours intravenously results in a mean serum trough concentration of 17.97 μg/ml (SD 8.02); the mean synovial trough concentration was 974.32 μg/ml (SD 547.50).[51]

Intra-articular antibiotic concentrations can vary significantly, yet show some comparability. Our patients had the same local medication regimen, with samples collected strictly at designated time points. In total, 390 samples were measured using HPLC. However, significant individual variation existed in intravenous antibiotic administration. We could not analyze bloodstream antibiotic concentrations or the impact of intravenous medication on intra-articular antibiotic concentrations.

Table II. Indicator differences before and after treatment.

Indicator	Total			Hip			Knee		
	Preoperative	Post-treatment	p-value	Preoperative	Post-treatment	p-value	Preoperative	Post-treatment	p-value
Median drainage, ml (IQR)	150.0 (100.0 to 310.0)	20.0 (0.0 to 55.0)	< 0.001*	260.0 (140.0 to 260.0)	12.5 (0.0 to 12.5)	< 0.001*	100.0 (75.0 to 137.5)	20.0 (5.0 to 65.0)	0.013*
Median synovial fluid leucocyte count, $10^{\wedge 6}$/l (IQR)	10,529.5 (5,098.3 to 17,856.0)	538.5 (267.3 to 1,393.5)	< 0.001*	8,487.0 (5,760.5 to 41,142.0)	675.0 (453.5 to 3,045.0)	< 0.001*	14,459.0 (5,655.5 to 15,636.5)	502.0 (184.0 to 555.3)	0.008*
Mean percentage of multinucleated cells, % (SD)	96.4 (2.0)	64.0 (25.4)	< 0.001†	95.9 (2.3)	68.5 (24.2)	0.009 †	96.9 (1.4)	59.4 (25.6)	0.002†
Mean ESR, mm/h (SD)	54.7 (12.4)	23.9 (11.0)	< 0.001†	56.0 (11.9)	24.9 (10.7)	< 0.001†	53.0 (13.0)	22.7 (11.4)	0.001†
Mean CRP, mg/l (SD)	40.8 (25.8)	12.0 (8.3)	< 0.001†	50.7 (22.4)	16.0 (7.8)	0.002 †	27.6 (24.1)	6.6 (5.6)	0.016†
Median BUN, µmol/l (IQR)	7.2 (5.6 to 10.8)	4.0 (3.0 to 5.3)	0.007 *	7.2 (4.6 to 11.4)	4.3 (2.8 to 16.3)	0.098 *	7.0 (5.9 to 7.0)	3.9 (3.2 to 4.5)	0.016*
Mean ALB, g/l (SD)	36.8 (3.5)	29.0 (2.9)	< 0.001†	36.7 (4.1)	27.9 (3.1)	< 0.001†	37.0 (2.5)	30.4 (1.5)	< 0.001†
Median creatinine, µmol/l (IQR)	67.5 (54.9 to 93.1)	58.0 (41.9 to 63.1)	< 0.001*	75.6 (62.2 to 96.8)	60.2 (53.4 to 73.5)	0.004 *	58.1 (54.9 to 60.3)	48.4 (36.3 to 52.4)	0.016*

*Wilcoxon test.
†Independent-samples *t*-test.
ALB, albumin; BUN, blood urea nitrogen.

The concentrations of vancomycin and meropenem decreased linearly within one to six hours after injection. Apart from the trough concentration in the knee joint on day 4, the remaining drug trough concentrations remained effective and stable throughout the treatment. We considered the following potential aetiologies for the observed phenomenon: initially, clinical observations indicate that vancomycin exhibits low solubility, with a propensity for drug precipitates at high concentrations. These precipitates may adhere to the inner walls of the injection tubing and could be dislodged during the aspiration of synovial fluid samples, resulting in anomalously elevated drug concentrations. Conversely, meropenem is typically well-soluble. On the other hand, the intra-articular environment in patients with PJI can vary significantly, which may also contribute to the large discrepancies in intra-articular concentration levels. Furthermore, the process of drug concentration measurement is inherently stable, and there is no conclusive evidence to suggest that the results are attributable to assay inaccuracies, although this possibility cannot be entirely discounted. This also suggests that during the process of local injections, it is imperative to ensure that the drug is as fully dissolved as possible to maintain the integrity of the tubing walls.

No statistically significant differences were observed between the two drugs in the hip and knee joints. The correlation analysis suggests that the amount of intraoperative bleeding and protein levels may be somewhat correlated with the peak drug concentration on the first day after surgery, but the specific factors of correlation could not be clearly identified due to the small sample size.

Although local administration of antibiotics is considered safe,[52] addressing safety concerns related to long-term postoperative high-concentration intra-articular antibiotic injections is crucial. High-concentration intra-articular antibiotic administration is an independent risk factor for acute kidney injury,[53,54] and these concentrations exhibit toxic effects on human cellular tissues. However, no specific cutoff values for local skeletal toxicity exist. Increased antibiotic concentration and exposure time lead to increased toxicity, resulting in decreased proliferative capacity of osteoblasts and chondrocytes.[55,56]

We observed a declining trend in albumin levels, which may indicate a potential adverse effect of high-concentration antibiotic administration. However, the overall clinical outcomes were positive, and no other signs of local antibiotic toxicity were detected. Our previous research, which includes a large number of patients who received local injections, has likewise not reported any significant local antibiotic toxic side-effects.[12-17]

In summary, intra-articular antibiotic injections for PJI treatment are effective and safe. Currently, there is a lack of related research into intra-articular antibiotic injections, and our study provides a basis for optimizing future treatment strategies. During long-term antibiotic therapy,

it is essential to monitor drug concentrations and patient conditions, adjusting treatment plans accordingly. One recent animal study suggested that topical medication is superior to intravenous administration, necessitating further validation through large-scale, controlled clinical trials.[57]

This study demonstrates that the intra-articular local administration of antibiotics has the advantage of maintaining high concentration levels of antibiotics for an extended period, and allows for the flexible adjustment of treatment plans according to the clinical situation. However, due to the absence of a control group, it was not possible to ascertain the concentration differences of the two routes of administration in blood and synovial fluid, nor to compare the treatment efficacy between the two methods. Further large-sample, controlled studies are required.

Supplementary material

Includes the high-performance liquid chromatography (HPLC) method for determining specific parameters of vancomycin and meropenem in synovial fluid.

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Funding statement

The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this work was supported by: Xinjiang Uygur Autonomous Region Natural Science Foundation (No. 2023D01C231); The National Natural Science Foundation of China (No. 82260435); Key Laboratory of High Incidence Disease Research in Xinjiang (Xinjiang Medical University), Ministry of Education-Key project (No. 2023A01); Major Special Projects of Science and Technology Plan of Xinjiang Uygur Autonomous Region (2022A03011); and Science and Technology Innovation Team Project of Xinjiang Uygur Autonomous Region Science and Technology Department (2023TSYCTD0014).

ICMJE COI statement

The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this work was supported by: Xinjiang Uygur Autonomous Region Natural Science Foundation (No. 2023D01C231); The National Natural Science Foundation of China (No.82260435); Key Laboratory of High Incidence Disease Research in Xinjiang (Xinjiang Medical University), Ministry of Education-Key project (No.2023A01); Major Special Projects of Science and Technology Plan of Xinjiang Uygur Autonomous Region (2022A03011); and Science and Technology Innovation Team Project of Xinjiang Uygur Autonomous Region Science and Technology Department (2023TSYCTD0014).

Data sharing

The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

Acknowledgements

We express our gratitude to the patients for their support and cooperation. Thanks to the research team, for their dedication. We appreciate colleagues and experts for their valuable insights and suggestions, and funding agencies for supporting this research. We would like to thank the Charlesworth Group for providing linguistic assistance during the preparation of this manuscript.

Ethical review statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (230412-11). Signed written informed consents were obtained from each participant prior to the commencement of the study.

Open access funding

The open access fee for this article was provided by the funding listed above.