RESEARCH ARTICLE

Elution and Biomechanical Properties of Meropenem-Loaded Bone Cement

Li-hong Wang, MD[1], Ya-dong Feng, MD[1], Xiao-wei Zhang, MD[2], Long Jin, MD[3], Fang-lun Zhou, MD[1], Guo-hong Xu, MD[1]

Department of [1]Orthopaedics, Dongyang People's Hospital, [2]Pathology, Dongyang People's Hospital and [3]Pharmacy, Dongyang People's Hospital, Wenzhou Medical University, Dongyang, China

Objective: To investigate the biomechanical and elution properties of meropenem-loaded bone cement.

Methods: Bone cement (Palacos LV) with 5% (2 g/4 0g), 10% (4 g/40 g), and 15% (6 g/40 g) meropenem; 5% (2 g/40 g) and 10% (4 g/40 g) vancomycin; and blank bone cement were prepared in a total of six groups named A2, A4, A6, B2, B4, and A0 (antibiotic-free). 36 cylinder specimens (6-mm diameter and 12-mm height) of all six groups were molded for a compression test. After the compression test, because of mechanical properties below the ISO standard requirements, groups B2, B4 were not subjected to a bending test. So a total of 24 rectangular strip specimens (10-mm width, 75-mm length, and 3.3-mm thickness) for groups A2, A4, A6 and A0 were molded for the bending test. Between-group differences of compressive strength, bending strength and bending modulus were analyzed. The meropenem standard was prepared as a series of standard solutions to calculate the standard curve. At a constant temperature of 37 °C, separately, meropenem-loaded bone cement cylinder specimens (12 mm in diameter and 17 mm in length) of A2, A4 and A6 were serially immersed in saline solution without stirring. The eluent drug concentration at 24, 48, 72 h and 6, 12, 24 days was measured and the drug concentration-time curve of meropenem was constructed.

Results: With the exception of groups B2 and B4, all cements compressive strength values were well above the minimum requirement of the ISO 5833 standard (70 MPa). The compressive strength and bending strength values of group A4 were higher than those of group A0 ($P < 0.05$), but no difference was found between the A0, A2 and A6 groups ($P > 0.05$). There were no intergroup differences of bending modulus between the A0, A2, A4 and A6 groups ($P > 0.05$). A standard curve of meropenem was obtained and a regression equation was constructed: $Y = 15.0265\ X + 13.5218$, $r = 1.00$. At 37 °C, the release of meropenem was rapid during the first 48 h for all A2, A4, A6 samples, and subsequent release continued to decrease.

Conclusion: When adding up to 15% (6 g/40 g) meropenem to the bone cement, the biomechanical properties were not reduced, and bone cement with 10% (4 g/40 g) meropenem had the best performance. At a constant temperature of 37°C, meropenem can be released from bone cement for up to 24 days.

Key words: Biomechanical phenomena; Bone cements; Kinetics; Meropenem; Vancomycin

Introduction

Although total hip arthroplasty and total knee arthroplasty are mature surgical techniques and are widely used around the world, it is undeniable that periprosthetic joint infection (PJI) is still one of the serious complications of total joint arthroplasty. PJI often means delays in patient recovery and increased hospital time and treatment costs. Because of the presence of bacterial biofilms

Address for correspondence Guo-hong Xu, MD, Department of Orthopaedics, Dongyang People's Hospital, Wenzhou Medical University, 60 Wuning West Road, Dongyang, China 322100 Tel: +8615924232897; Fax: +86579 86856121; Email: xgh316@163.com

Grant Sources: This research was supported by Natural Science Foundation of Zhejiang Province, China (LGF18H060001, awarded to Li-Hong Wang).
Disclosure: On behalf of all authors, the corresponding author states that there is no conflict of interest.
Received 2 April 2021; accepted 29 June 2021

Orthopaedic Surgery 2021;13:2417–2422 • DOI: 10.1111/os.13139

Orthopaedic Surgery

and drug resistance, the treatment of PJI is challenging[1,2]. For patients, PJI also often means re-surgery, as well as a great deal of stress and fear. Debridement is often needed to remove the biofilm, followed by total joint revision, including one-stage and two-stage revision arthroplasty[3].

There are various options for treating periprosthetic joint infection (PJI). For early acute periprosthetic infections, debridement, antibiotics and implant retention (DAIR) is maybe an effect way, but without doubt, bacteria drug resistance affects the outcome of DAIR[4]. Although one-stage revision has had success in many medical centers, and even been reported an effective way for chronic PJI[5], two-stage revision has been accepted by many scholars. Antibiotic-loaded cement spacers for local administration is a standard method in two-stage revision, and its success rate is close to 90%[6–8]. For two-stage revision arthroplasty and spacer exchange, not all antibiotics are suitable for loading to bone cement. Among them, gentamicin and vancomycin are the two most common antibiotics used in the treatment of PJI[9]. For Gram-positive bacteria, especially *Staphylococcus aureus* infections, vancomycin-loaded cement spacers show excellent therapeutic effects and are widely used in the revision of PJI.

Although Gram-positive bacteria play an important role in PJIs[10], Gram-negative bacterial infections are not uncommon, and are increasing[11–13]. Furthermore, PJIs related to anaerobes have also been reported[14,15]. For Gram-negative bacteria PJI, gentamicin is another antibiotic widely used in combination with bone cement. However, gentamicin resistance has become increasingly prominent[16], and gentamicin is usually ineffective for most anaerobic infections. In addition to culture-positive PJI, there is another clinical situation, which is culture-negative PJI[5]. For culture-negative PJI, antibiotics loaded to bone cement probably need to cover positive bacteria, drug-resistant negative bacteria and anaerobes. Is there a more efficient antibiotic-loaded cements for PJIs involving drug-resistant Gram-negative and anaerobes, and what is the best proportions for antibiotic and bone cement? These are urgent questions.

Meropenem is a water-soluble powder, which is stable on heating, ionizing radiation and causes less allergic reactions[17–19]. Some current research shows that meropenem has a broad antimicrobial spectrum. Meropenem has antibacterial effects on most of the Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Haemophilus influenzae*, and some anaerobic bacteria[20–22]. However, there are only a few reports about the application of meropenem-loaded bone cement in humans[23]. Samuel *et al.*[20] had reported the elution kinetics and bio-activity of meropenem-loaded bone cement with a maximum content of 10%, however, the biomechanical properties have not been studied. In previous studies, meropenem was often only used as a compounding factor in vancomycin-loaded bone cement[24,25]. And as far as we know, there are few separate studies on the biomechanical properties of meropenem bone cement. Based on the previous studies, whether the biomechanical properties of bone cement loaded with meropenem is up to standard, and whether higher content of meropenem (more than 10%) can be loaded to bone cement, it is not clear. The current study sought to: (i) summarize the biomechanical properties of meropenem-loaded bone cement; (ii) explore the best proportions for meropenem-loaded bone cement; and (iii) measure the eluent drug concentration of meropenem through high performance liquid chromatography and to study the elution kinetics.

Materials and Methods

PMMA

Commercial polymethyl methacrylate (PMMA) bone cement (Palacos LV, 40g powder +20mL liquid, Heraeus medical GmbH, Germany) was chosen as a control and as the basic material for the antibiotic admixture.

Antibiotics

Commercial vancomycin (Vianex, Patras, Greece) and meropenem (CSPC Pharmaceutical Group Limited, Hong Kong) were tested in terms of their effect on the mechanical behavior of PMMA bone cement. Subsequently, the elution properties of meropenem-loaded bone cement were investigated.

Under aseptic conditions, vancomycin or meropenem powder was mixed with PMMA powder for 2 min using an OmoMix mixer (Tecres, Italy), and then PMMA liquid was added to prepare antibiotic-loaded cement. The components were mixed evenly at 23 ± 1°C with humidity between 40% and 60%.

Grouping

Based on different proportions of antibiotics and PMMA powder, six formulations were investigated: (i) bone cement without antibiotics (control, A0); (ii) bone cement with 5% (2 g/40 g) meropenem (A2); (iii) bone cement with 10% (4 g/40 g) meropenem (A4); (iv) bone cement with 15% (6 g/40 g) meropenem (A6); (v) bone cement with 5% (2 g/40 g) vancomycin (B2); and (vi) bone cement with 10% (4 g/40 g) vancomycin (B4). The bone cement with 15% (6 g/40 g) vancomycin was powdery and could not be made into dough, so it was not used. The mass percent refers to the amount of antibiotics added to the PMMA powder, excluding the PMMA liquid.

Specimens for Biomechanical Tests

Specimens were produced by molding, for each formulation, six specimens were molded. A total of 36 compression test specimens for all six groups were obtained. The specimens were cylinders of 6-mm diameter and 12-mm height. After the compression test, because of mechanical properties below the ISO standard requirements, groups B2, B4 were not subjected to the bending test.

The specimens for the bending test were rectangular strips of 10-mm width, 75-mm length, and 3.3-mm thickness. A total of 24 bending test specimens for formulation

A2, A4, A6 and A0 were obtained. Specimens were stored at 23 ± 1°C for 24 ± 2 h before testing, according to ISO 5833 standard recommendations.

Compression and Bending Tests

The compression tests were carried out at a cross-head rate of 20 mm/min using an electronic universal testing machine (WDW-50J; Jinan East Testing Machine, Jinan, China). Four-point bending tests were performed in another materials testing machine (Mini Bionix 858; MTS Systems, Minneapolis, MN, USA), at a rate of 5 mm/min. For each formulation and each type of test, six specimens were tested, and the average value of compressive strength, bending strength and bending modulus was calculated.

Compressive Strength

Under normal temperature, the maximum compression a material can withstand per unit area without failure. It is usually expressed in N/mm^2, that is, MPa. According to ISO 5833, the compressive strength of bone cement should be higher than 70 MPa.

Bending Strength

Bending strength is defined as the maximum stress that a material exhibits at failure due to a three or four-point flexural load. It is an ability of materials to resist bending deflection when energy is applied to the structure. According to ISO 5833, the bending strength of bone cement should be more than 50 MPa. Four-point bending tests were performed in this study.

Bending Modulus

Bending modulus refers to the ability of a material to resist bending deformation within the elastic limits. It is also described in terms of flexural deformation, the ratio of stress to strain. The bending modulus of bone cement should be higher than 1800 MPa according to ISO 5833.

Standard Curve of Meropenem

The meropenem standard (National Institutes for Food and Drug control, China) was prepared as a series of standard solutions of 0.0875, 8.7478, 87.4785, 437.3925 and 874.7850 μg/mL. The peak areas of the standard solutions were measured quantitatively. The drug concentrations and peak areas were analyzed through linear regression to calculate the standard curve.

Elution Specimens of Meropenem-Loaded Bone Cement and Sampling

In sterile conditions, three cylinder specimens (12 mm in diameter and 17 mm in length) were molded for each group of A2, A4 and A6.

At a constant temperature of 37 °C, A2, A4 and A6 specimens were immersed separately in sterile containers with 100 mL of saline solution without stirring. Sampling was performed at 24, 48, 72 h and 6, 12, 24 days after immersion. Before sampling, the container was placed on a magnetic stirrer for 1 min, and then 1.5 mL of solution was removed and analyzed. The specimens were then separately rinsed with 10 mL of saline solution and immersed in new containers with 100 mL of saline solution.

Elution Drug Concentration of Meropenem

Samples were assayed through high performance liquid chromatography (Agilent Technologies, Santa Clara, CA, USA) at a constant temperature of 25°C with a reverse-phase column (Waters Symmetry C18, 4.6 × 150 mm, 5 μm). The mobile phase consisted of 10mmol/L potassium dihydrogen phosphate solution and acetonitrile at a ratio of 93.5:6.5 v/v and the flow was 1.0 mL/min. Meropenem was detected using an ultraviolet detector at 298 nm, and the run time was 25 min. The limit of quantitation was 0.0875 μg/mL. All the samples were analyzed immediately on the day of collection. Values of the concentration of meropenem were obtained for each sample. Three specimens were tested in each group, and the average value was calculated. The eluent drug concentration at 24, 48, 72 h and 6, 12, 24 days was measured and the drug concentration-time curve of meropenem eluted from bone cement was constructed.

Statistical Analysis

Continuous variables were presented as the mean ± standard derivation. Between-group differences were analyzed by analysis of variance (ANOVA). A series of meropenem standard solutions were assayed and simple linear regression analysis was performed. The difference was considered significant if the *P* value was less than 0.05. All statistics were performed with SPSS version 18.0 (SPSS, Chicago, IL, USA).

Results

Compressive Strength

With the exception of Group B2 ((68.61 ± 4.91) MPa) and B4 ((56.76 ± 5.19) MPa), all cements compressive strength values were well above the minimum requirement of ISO 5833 (70 MPa). The compressive strength of group A4

TABLE 1 Compressive strength, bending strength and bending modulus values (MPa) of all formulation antibiotic-loaded cement samples tested

Samples	Compressive strength	Bending strength	Bending modulus
A0	93.28 ± 3.84*	64.12 ± 4.56*	2402.74 ± 122.37*
A2	97.39 ± 3.66*#	67.85 ± 4.05*#	2465.22 ± 140.95*
A4	101.19 ± 1.31#	70.69 ± 1.27#	2473.28 ± 71.05*
A6	94.44 ± 2.90*	65.28 ± 2.45*	2416.19 ± 137.63*
B2	68.61 ± 4.91	/	/
B4	56.76 ± 5.19	/	/
F	138.56	4.57	0.50
P	<0.001	0.01	0.69

* or #: Not statistically significant between groups with the same sign ($P > 0.05$).

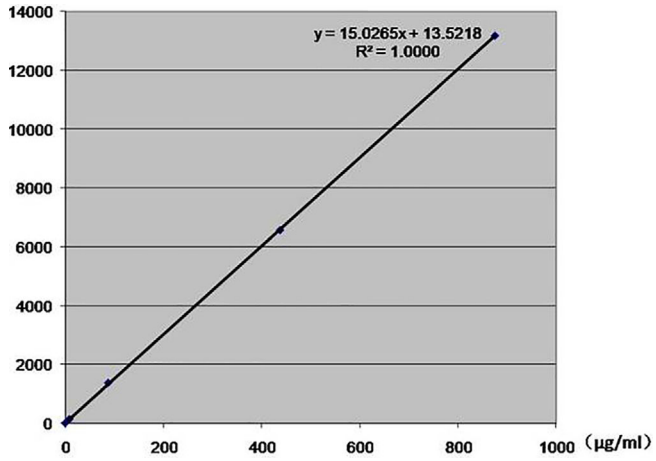

Fig. 1 The standard curve and regression equation of the meropenem standard solutions.

TABLE 2 Elution drug concentration (Mean ± standard deviation) of meropenem (μg/mL) at 37°C

Time (d)	Sample A2	Sample A4	Sample A6
1	29.16 ± 3.14	60.05 ± 7.45	95.42 ± 7.96
2	5.12 ± 0.63	9.99 ± 1.39	14.80 ± 0.98
3	2.27 ± 0.58	4.30 ± 0.27	6.69 ± 1.51
6	2.10 ± 0.39	4.05 ± 0.51	6.31 ± 1.36
12	1.02 ± 0.57	1.96 ± 0.25	2.87 ± 0.74
24	0.36 ± 0.19	0.62 ± 0.20	1.01 ± 0.12

((101.19 ± 1.31) MPa) were higher than those of group A0 ((93.28 ± 3.84) MPa) ($F = 138.56$, $P < 0.05$), but no difference was found between the A0, A2 and A6 groups ((93.28 ± 3.84), (97.39 ± 3.66), and (94.44 ± 2.90) MPa) ($P > 0.05$) (Table 1).

Bending Strength

The compressive strength values of Group B2 and B4 were lower than the minimum requirement of ISO 5833 (70 MPa), so no subsequent bending test was carried out for Group B2 and B4. The bending strength values of group A4 ((70.69 ± 1.27) MPa) were higher than those of group A0 ((64.12 ± 4.56) MPa) ($F = 4.57$, $P < 0.05$), but no difference was found between the A0, A2 and A6 groups ((64.12 ± 4.56), (67.85 ± 4.05), and (65.28 ± 2.45) MPa) ($P > 0.05$). All the bending strength values of A0, A2, A4 and A6 groups were well above the minimum requirement of ISO 5833 (50 MPa) (Table 1).

Bending Modulus

All the bending modulus values of A0, A2, A4 and A6 groups ((2402.74 ± 122.37), (2465.22 ± 140.95), (2473.28 ± 71.05), and (2416.19 ± 137.63) MPa) were well above the minimum requirement of ISO 5833 (1800 MPa). There were no intergroup differences of bending modulus between the A0, A2, A4 and A6 groups ($F = 0.50$, $P > 0.05$) (Table 1).

Standard Curve of Meropenem and Regression Equation

A series of meropenem standard solutions of 0.0875, 8.7478, 87.4785, 437.3925 and 874.7850 μg/mL were assayed through high performance liquid chromatography. A standard curve

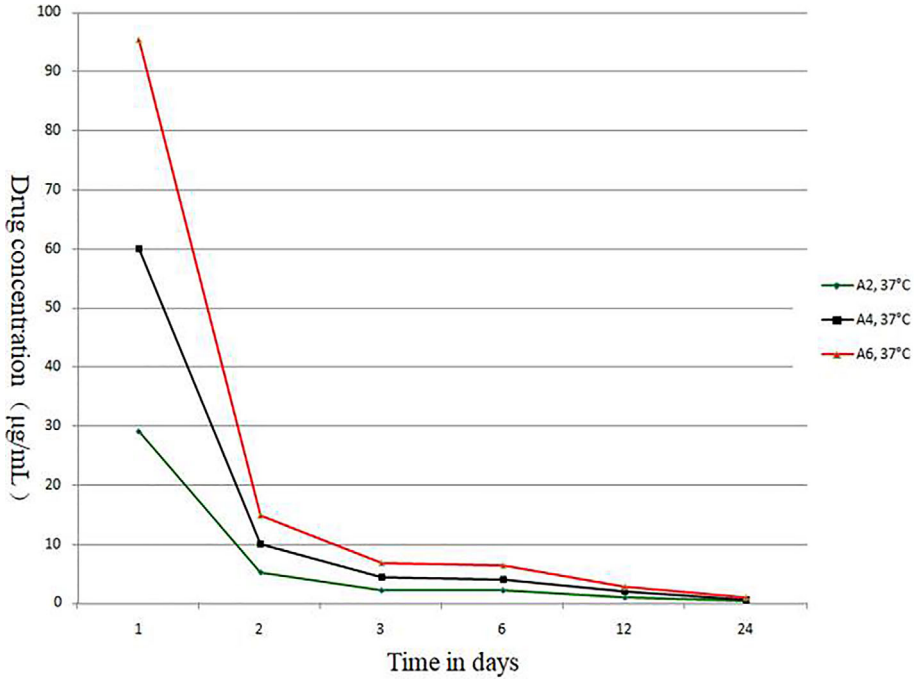

Fig. 2 Drug concentration-time curve of meropenem eluted from meropenem-loaded bone cement samples.

(Fig. 1) was obtained and a regression equation for the meropenem standard solutions was constructed: $Y = 15.0265\ X + 13.5218$, $r = 1.00$. The limit of quantitation was 0.0875 μg/mL.

Elution Drug Concentration of the Meropenem

At different time-points of 24, 48, 72 h and 6, 12, 24 days, the mean concentration of eluted meropenem for samples A2, A4, A6 at 37°C is presented in Table 2. At 24 days of immersion, the eluted meropenem concentration of samples A2, A4, A6 was respectively (0.36 ± 0.19), (0.62 ± 0.20) and (1.01 ± 0.12) μg/mL. Figure 2 shows the elution concentrations of meropenem at different sampling times at 37°C. The release of meropenem was rapid during the first 48 h. After 48 h, the meropenem concentration of samples A2, A4, A6 continued to decrease throughout the remainder of the study period.

Discussion

Because of bacterial resistance and the emergence of anaerobic PJIs, it is especially important to explore new antibiotic-loaded cements for PJIs involving Gram-negative bacteria and anaerobes. The current study summarized the elution and biomechanical properties of meropenem-loaded bone cement. When adding no more than 15% (6 g/40 g) meropenem to bone cement, the biomechanical properties are not reduced. Among the tested specimens, bone cement with 10% (4 g/40 g) meropenem (A4) demonstrated the best characteristics. The biomechanical properties of meropenem-loaded bone cement were better than those of vancomycin-loaded bone cement (with the same drug content). When the 5%, 10% and 15% meropenem-loaded bone cement was immersed in saline solution at 37°C, meropenem was effectively released for at least 24 days.

Biomechanical Properties and the Best Proportions of Meropenem-Loaded Bone Cement

It is generally believed that the mechanical properties of bone cement will be affected by the addition of antibiotics[26,27]. Moreover, different antibiotics can have different effects. For example, the performance of cefazolin-loaded bone cement was worse than that of vancomycin-loaded bone cement, with the same drug content[28]. Although vancomycin is considered a classical antibiotic in terms of compounding with bone cement, it also reduces the compression and fatigue strength of bone cement[29]. Similarly, in the current study, when 5%–10% vancomycin was added, the compressive strength of vancomycin-loaded bone cement were below the ISO standard requirements. On the contrary, when adding no more than 15% (6 g/40 g) meropenem to bone cement, the biomechanical properties were not reduced. This was similar to the study of Persson *et al.*[25], but in their study, the content of meropenem in bone cement was relatively small, only 1.25% (w / w). In our study, the compressive strength and bending strength values of bone cement with 10% (4 g/40 g) meropenem were even higher than those of the control bone cement. At present, the mechanism underlying this "paradox" is not clear and further research is needed.

Elution Kinetics

There are some reports about meropenem-loaded bone cement and its elution process[20,22]. However, meropenem was often only used as a compounding factor in vancomycin-loaded bone cement[24]. Andollina *et al.* confirmed the bactericidal effect of meropenem-loaded bone cement on *Pseudomonas aeruginosa* and *Escherichia coli in vitro*, the authors described the elution process of vancomycin but not meropenem[21]. Samuel *et al.*[20] had reported the elution kinetics and bio-activity of meropenem-loaded bone cement with a maximum content of 10%, and the elution process was analogous to our study. We observed the elution process of meropenem-loaded bone cement with 5%, 10% and 15% content. At 37°C, the elution process of meropenem-loaded bone cement was similar to the previous elution process of vancomycin-loaded bone cement[21]. Within 48 h, meropenem was rapidly eluted from bone cement, and then the elution rate became slow with time. Moreover, after 24 days of immersion, the concentration of meropenem in the eluate was still higher than the minimum bactericidal concentration for common bacteria, as reported in the literature, such as methicillin-sensitive *S aureus*, *P. aeruginosa*, *E. coli*, and *K.pneumoniae*[20]. In addition, for complex PJIs, some researchers have added meropenem into vancomycin-loaded bone cement. The results showed that adding meropenem to vancomycin-loaded bone cement could expand the anti-bacterial spectrum, and improve the success rate of treatment[30].

Limitation

Our study has some limitations. First, in the current study, with the increase in the proportion of antibiotics (particularly vancomycin), the antibiotic-loaded bone cements gradually thickened from a paste to a powder. It was impossible to prepare samples of bone cement with 15% (6 g/40 g) vancomycin. Second, in terms of biomechanical properties, bone cement with 10% (4 g/40 g) meropenem was the first choice, but the mechanism is not clear and further research is needed. Third, previous studies have confirmed the antibacterial effect of bone cements loaded with meropenem[20,22]. Therefore, we have not repeated the relevant study.

Conclusions

In conclusion, the present *in vitro* study revealed the excellent biomechanical properties of meropenem-loaded bone cement. At a constant temperature of 37 °C, meropenem can be released from bone cement for up to 24 days. Meropenem-loaded bone cement maybe an effective method for the treatment of PJI caused by Gram-negative bacteria and anaerobes.

Author Contributions

Li-Hong Wang and Guo-Hong Xu developed the study concept. Li-Hong Wang wrote the initial draft of the manuscript. Ya-Dong Feng and Xiao-Wei Zhang performed the data extraction and analyses. Li-Hong Wang and Fang-Lun Zhou designed the study and contributed to revisions of the manuscript. Long Jin provided interpretations for the

results together with Guo-Hong Xu. All co-authors made substantial contributions to the paper and approved the final manuscript.

Availability of Data and Materials

The data supporting the conclusions of this study are included within the article.

References

1. Mandell JB, Orr S, Koch J, *et al*. Large variations in clinical antibiotic activity against *Staphylococcus aureus* biofilms of periprosthetic joint infection isolates. J Orthop Res, 2019, 37: 1604–1609.
2. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science, 1999, 284: 1318–1322.
3. Konrads C, Franz A, Hoberg M, Rudert M. Similar outcomes of two-stage revisions for infection and one-stage revisions for aseptic revisions of knee endoprostheses. J Knee Surg, 2019, 32: 897–899.
4. Rudelli BA, Giglio PN, de Carvalho VC, *et al*. Bacteria drug resistance profile affects knee and hip periprosthetic joint infection outcome with debridement, antibiotics and implant retention. BMC Musculoskelet Disord, 2020, 21: 574.
5. van den Kieboom J, Tirumala V, Box H, Oganesyan R, Klemt C, Kwon YM. One-stage revision is as effective as two-stage revision for chronic culture-negative periprosthetic joint infection after total hip and knee arthroplasty. Bone Joint J, 2021, 103: 515–521.
6. Akhtar A, Mitchell C, Assis C, Iranpour F, Kropelnicki A, Strachan R. Cement pedestal spacer technique for infected two-stage revision knee arthroplasty: description and comparison of complications. Indian J Orthop, 2019, 53: 695–699.
7. Biring GS, Kostamo T, Garbuz DS, *et al*. Two-stage revision arthroplasty of the hip for infection using an interim articulated Prostalac hip spacer: a 10- to 15-year follow-up study. J Bone Joint Surg Br, 2009, 91: 1431–1437.
8. Tian MQ, Yang XT, Tian XB, Sun YB, Duan YH, Sun L. Short-term follow-up of antibiotic-loaded articulating cement spacers in two-stage revision of infected total knee arthroplasty: a case series. Orthop Surg, 2018, 10: 128–133.
9. Iarikov D, Demian H, Rubin D, Alexander J, Nambiar S. Choice and doses of antibacterial agents for cement spacers in treatment of prosthetic joint infections: review of published studies. Clin Infect Dis, 2012, 55: 1474–1480.
10. Honkanen M, Jamsen E, Karppelin M, *et al*. Periprosthetic joint infections as a consequence of bacteremia. Open Forum Infect Dis, 2019, 6: ofz218.
11. Schrama JC, Lutro O, Langvatn H, *et al*. Bacterial findings in infected hip joint replacements in patients with rheumatoid arthritis and osteoarthritis: a study of 318 revisions for infection reported to the Norwegian Arthroplasty Register. ISRN Orthop, 2012, 2012: 437675.
12. Lutro O, Langvatn H, Dale H, *et al*. Increasing resistance of coagulase-negative staphylococci in Total hip arthroplasty infections: 278 THA-revisions due to infection reported to the Norwegian Arthroplasty Register from 1993 to 2007. Adv Orthop, 2014, 2014: 580359.
13. Rodriguez-Pardo D, Pigrau C, Lora-Tamayo J, *et al*. Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study. Clin Microbiol Infect, 2014, 20: 911–919.
14. Kierzkowska M, Pedzisz P, Babiak I, *et al*. Orthopedic infections caused by obligatory anaerobic gram-negative rods: report of two cases. Med Microbiol Immunol, 2017, 206: 363–366.
15. Zafar Y, Elkafrawy AA, Nahar J, *et al*. Acalculous cholecystitis presenting as a septic joint: a case report. Cureus, 2019, 11: e5193.
16. Memish ZA, Shibl AM, Kambal AM, Ohaly YA, Ishaq A, Livermore DM. Antimicrobial resistance among non-fermenting gram-negative bacteria in Saudi Arabia. J Antimicrob Chemother, 2012, 67: 1701–1705.
17. Mendez AS, Dalomo J, Steppe M, *et al*. Stability and degradation kinetics of meropenem in powder for injection and reconstituted sample. J Pharm Biomed Anal, 2006, 41: 1363–1366.
18. Kilinska K, Cielecka-Piontek J, Skibinski R, *et al*. The radiostability of meropenem trihydrate in solid state. Molecules, 2018, 23: 2738.
19. Schmid M, Steiner O, Fasshold L, Goessler W, Holl AM, Kühn KD. The stability of carbapenems before and after admixture to PMMA-cement used for replacement surgery caused by gram-negative bacteria. Eur J Med Res, 2020, 25: 34.
20. Samuel S, Mathew BS, Veeraraghavan B, Fleming DH, Chittaranjan SB, Prakash JAJ. In vitro study of elution kinetics and bio-activity of meropenem-loaded acrylic bone cement. J Orthop Traumatol, 2012, 13: 131–136.
21. Andollina A, Bertoni G, Zolezzi C, *et al*. Vancomycin and meropenem in acrylic cement: elution kinetics of in vitro bactericidal action. Chir Organ Mov, 2008, 91: 153–158.
22. Morejon Alonso L, Fernandez Torres I, Zayas Tamayo AM, *et al*. Antibacterial effect of acrylic bone cements loaded with drugs of different action's mechanism. J Infect Dev Ctries, 2019, 13: 487–495.
23. Solomon AW, Stott PM, Duffy K, Kumar PGA, Holliman RE, Bridle SH. Elution and antibacterial activity of meropenem from implanted acrylic bone cement. J Antimicrob Chemother, 2010, 65: 1834–1835.
24. Baleani M, Persson C, Zolezzi C, Andollina A, Borrelli AM, Tigani D. Biological and biomechanical effects of vancomycin and meropenem in acrylic bone cement. J Arthroplasty, 2008, 23: 1232–1238.
25. Persson C, Baleani M, Guandalini L, Tigani D, Viceconti M. Mechanical effects of the use of vancomycin and meropenem in acrylic bone cement. Acta Orthop, 2006, 77: 617–621.
26. Li T, Fu L, Wang J, Shi Z. High dose of vancomycin plus gentamicin incorporated acrylic bone cement decreased the elution of vancomycin. Infect Drug Resist, 2019, 12: 2191–2199.
27. Shiels SM, Tennent DJ, Akers KS, Wenke JC. Determining potential of PMMA as a depot for rifampin to treat recalcitrant orthopaedic infections. Injury, 2017, 48: 2095–2100.
28. Paz E, Sanz-Ruiz P, Abenojar J, Vaquero-Martín J, Forriol F, del Real JC. Evaluation of elution and mechanical properties of high-dose antibiotic-loaded bone cement: comparative "in vitro" study of the influence of Vancomycin and Cefazolin. J Arthroplasty, 2015, 30: 1423–1429.
29. Bishop AR, Kim S, Squire MW, Rose WE, Ploeg HL. Vancomycin elution, activity and impact on mechanical properties when added to orthopedic bone cement. J Mech Behav Biomed Mater, 2018, 87: 80–86.
30. Yang C, Wang J, Yin Z, *et al*. A sophisticated antibiotic-loading protocol in articulating cement spacers for the treatment of prosthetic joint infection: a retrospective cohort study. Bone Joint Res, 2019, 8: 526–534.