CLINICAL SCIENCE

INFLUENCE OF VANCOMYCIN AND MEROPENEM LOADING ON COMPRESSIVE STRENGTH OF POLYMETHYL METHACRYLATE BONE CEMENT

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Citation: Popovska D, Avramov N, Samardziski M, Shabani I, Andonovski A, Bogojevska Doksevska M, Stojmenski S. Influence of vancomycin and meropenem loading on compressive strength of polymethyl methacrylate bone cement Arch Pub Health 2025; 17 (1).

doi.org/10.3889/aph.2025.6141

Online First

Key words: antibiotic-loaded bone cement, meropenem, vancomycin, compressive strength

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Received: 29-Nov-2024; **Revised:** 15-Feb-2025; **Accepted:** 17-Feb-2025; **Published:** 24-Feb-2025

Competing Interests: The author have declared that no competing interests

Abstract

The rise of antibiotic resistance of certain bacteria to commonly used agents in antibiotic- loaded polymethyl methacrylate (PMMA) bone cement has led to the search for new antibiotic agents. A potential problem in introducing new antibiotics into the PMMA mixture is disruption of the mechanical properties of bone cement, which is intended for mechanical fixation of joint implants. The aim of this study was to test compressive strength of bone cement loaded with vancomycin, meropenem or their combination. Materials and methods: Five groups of samples (PMMA, PMMA+2.5%w/w vancomycin, PMMA+2.5%w/w meropenem, PMMA+1.25%w/w vancomycin and 1.25%w/w meropenem and PMMA+2.5%w/w vancomycin and 2.5%w/w meropenem) were prepared and tested for compressive strength according to specifications of the ISO5833:2002 international standard. Results: All tested groups had compressive strength significantly above the minimum value of 70 MPa set by the standard (87.9 – 98.6MPa, p<.0001). All groups of antibiotic-loaded bone cement had significantly lower compressive strength than PMMA. Conclusion: All tested groups met the basic compressive strength criteria for clinical use in arthroplasty procedures.

КЛИНИЧКИ ИСТРАЖУВАЊА

ВЛИЈАНИЕ НА ВАНКОМИЦИНОТ И МЕРОПЕНЕМОТ ВРЗ МЕХАНИЧКИТЕ КАРАКТЕРИСТИКИ НА ПОЛИМЕТИЛМЕТАКРИЛАТЕН КОСКЕН ЦЕМЕНТ

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Цитирање: Поповска Д, Аврамов Н, Самарџиски М, Шабани И, БАндоновски А, Богојевска Докевска М, Стојменски С. Влијание на ванкомицинот и меропенемот врз механичките карактеристики на полиметилметакрилатен коскен цемент Арх Ј Здравје 2025;17 (1)

doi.org/10.3889/aph.2025.6141
Online First

Клучни зборови: коскен цемент, ванкомицин, меропенем, максимална јакост на притисок

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Примено: 29-ное-2024; **Ревидирано:**15-фев-2025; **Прифатено:** 17-фев-2025; **Објавено:** 24-фев-2025

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Порастот на антиботската резистенција на бактериите на вообичаените агенси кои се користат во полиметилметакрилатен (ПММА) цемент како метод за локално доставување на високи дози на антибиотик во ендопротетиката предизвикува интерес за воведување на нови антибиотици. Проблем при користењето на антибиотици е нарушувањето на механичките карактеристики на цементот. Целта на ова истражување беше процена на максималната јакост на компресија на коскен цемент со додадени различни количини ванкомицин и меропенем. Материјали и методи: Пет групи на примероци (чист ПММА, ПММА со 2,5% ванкомицин, ПММА со 2,5% меропенем, ПММА со 1,25% ванкомицин и 1,25% меропенем и ПММА со 2,5% ванкомицин и 2,5% меропенем) беа подготвени и тестирани за максимална јакост на притисок според спецификацијата на меѓународниот стандард ISO5833:2002. Резултати: Сите групи на тестирани примероци имаа значително поголема максимална јакост на притисок во однос на минимално одредената граница од 70 MPa (87.9 – 98.6MPa, p<.0001). Групите со додадени антибиотици имаа сигнификантно пониска јакост во однос на групата без антибиотик. Заклучок: Во однос на максималната јакост на притисок, сите испитани формулации во оваа студија ги задоволуваат основните критериуми за клиничка употреба при процедурите на артропластика.

Introduction

Antibiotic loading of polymethyl methacrylate (PMMA) bone cement is an established practice in joint replacement surgery. Gentamycin-loaded PMMA is commercially available from numerous brands. Prophylactic use of antibiotic-loaded bone cement (ALBC) has become more frequent due to the results of studies based on the Norwegian arthroplasty register, which showed that combined use of systemic antibiotic and ALBC for implant fixation in total hip replacement leads to lower revision rates compared to using systemic antibiotic or ALBC alone.[1,2] Many studies indicate that the revision risk for total hip arthroplasty is similar for cemented and non-cemented implants, but the risk is higher for cemented implants where bone cement without antibiotics is used.[3–5]

The increasing prevalence of multiresistant bacterial strains causes decrease in the efficacy of established ALBC preparations containing gentamycin. Therefore, there is interest in developing ALBC with different antibiotic combinations.[6,7] One of the challenges of adding antibiotics to bone cement is alteration of mechanical properties of the cement, which are critical when used for implant fixation.[8] The International Organization for Standardization (ISO, Geneva, Switzerland) defines compressive strength as one of the key indicators of the mechanical properties of polymerized cements, setting a requirement that all commercially available bone cements must withstand a compression force of at least 70 MPa.[9]

The aim of this study was to test the compressive strength of bone cement loaded with vancomycin, meropenem or their combination, and to determine whether the tested combinations meet the compressive strength requirements for use in implant fixation.

Materials and methods

We conducted an experimental study, in which we tested the compressive strength of the commercially available bone cement Smart Set Endurance™ MV (DePuy Synthes) loaded with vancomycin and meropenem for intravenous use in powder form. All tested samples were manufactured from the same cement series with LOT number 3684077. We produced and tested five groups of samples with the following antibiotic combinations:

1. PMMA group – control group without antibiotic
2. V 2.5% - 40 g PMMA with 1 g vancomycin
3. M 2.5% - 40 g PMMA with 1 g meropenem
4. VM 2.5% - 40 g PMMA with 0.5 g vancomycin and 0.5 g meropenem
5. VM 5% - 40 g PMMA with 1 g vancomycin and 1 g meropenem

For all groups of samples, we tested the compressive strength as the maximum compressive force before plastic deformation of cylindric specimens occurs, following the instructions of the ISO5833:2002, Annex E - Determination of compressive strength of polymerized cement.[9]

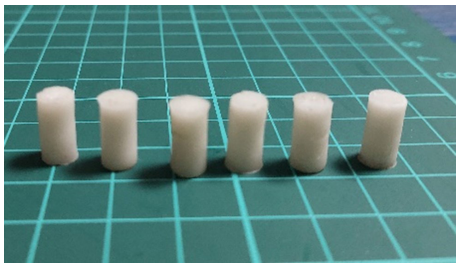
We prepared a total of 50 samples, with 10 samples per each group. We prepared the bone cement ac-

cording to packaging instructions. Cement mixing was performed in sterile conditions, at a temperature of 23±1°C. In all groups containing antibiotics, the powder component of the bone cement was mixed with the antibiotic powder and then the liquid component of the cement was added. The mixture was stirred with a spatula until a gloved finger with a sterile unpowdered latex glove separated cleanly from the cement. Then stainless-steel moulds (Figure 1 A.) were filled with the cement dough and clamped with end plates. After one hour of cement setting, the molds were unclamped, the excess cement was removed with an abrasive, and the specimens were removed with removal rods.

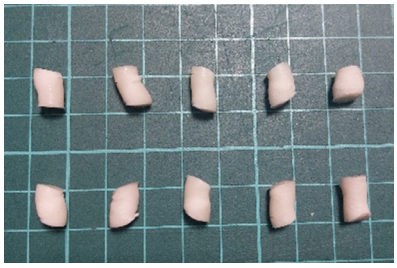
The samples for compressive strength testing were cylinders of length 12 (±0.1) mm and diameter 6 (±0.1) mm (Figure 1). They were stored in air for 24 hours, at a temperature of 23±1°C. Six samples were discarded due to visible defects in shape and filling. The average diameter of each test piece was measured, taking the measurements in two mutually perpendicular directions for two sections. This data was used to calculate the average diameter, sample surface, and volume. All samples were weighted, and density was calculated as the ratio of mass to volume.

Figure 1. A. Molds for sample preparation. B. Cylindrical samples with 6 mm diameter and 12 mm height, group PMMA. C. VM 2.5% samples after testing

A.



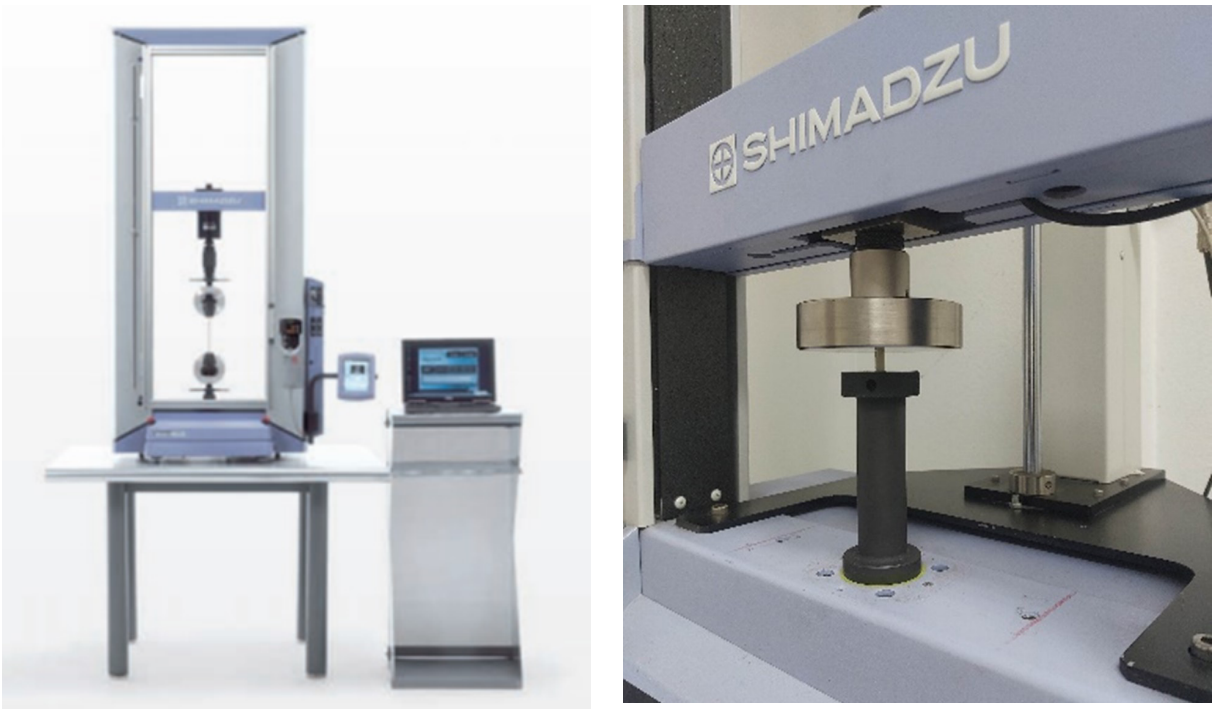
B.



C.

Compressive strength was tested for the remaining 44 samples at the Laboratory for material testing at Faculty of Mechanical Engineering, Ss. Cyril and Methodius University in Skopje using Shimadzu AGS-X 10kN materials testing machine with a speed range 0.001 to 1000 mm/min (Figure 2). The testing was performed at a cross-head rate of 23 mm/min. Data on force (N) and stroke (mm) were collected and compressive strength was calculated in MPa (N/mm^2). Figure 3 shows the output of the testing machine with the compressive strength graph. Two samples (from groups V 2.5% and M 2.5%) were ejected of the machine during compression, and results for these samples were excluded from the analysis.

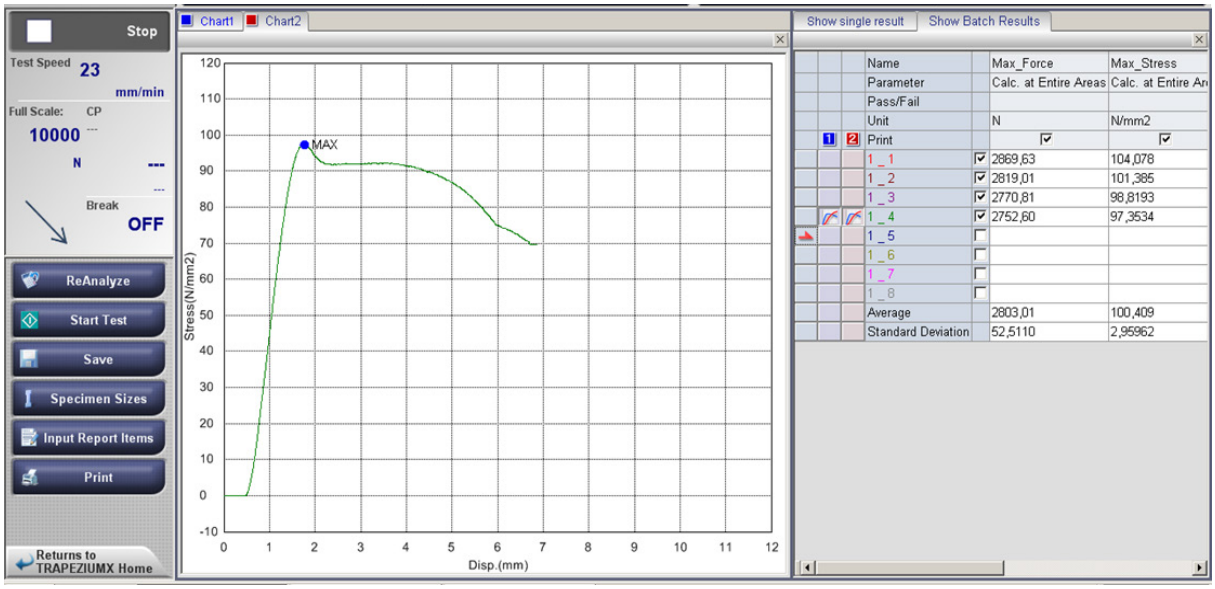
Figure 1. A. Shimadzu AGS – X materials testing machine. B. A sample set for testing in the materials testing machine



A. B.

The data were analyzed for a total of 42 samples with XLStat software for Excel (Lumivero (2024). XLSTAT statistical and data analysis solution. https://www.xlstat.com/en.) The results were examined with one-sample t-tests and analysis of variance (ANOVA) with post-hoc tests. We used alpha level of .05 for all statistical tests.

Figure 3. Output with graph for force/stoke relationship for sample 4 from PMMA group



Results

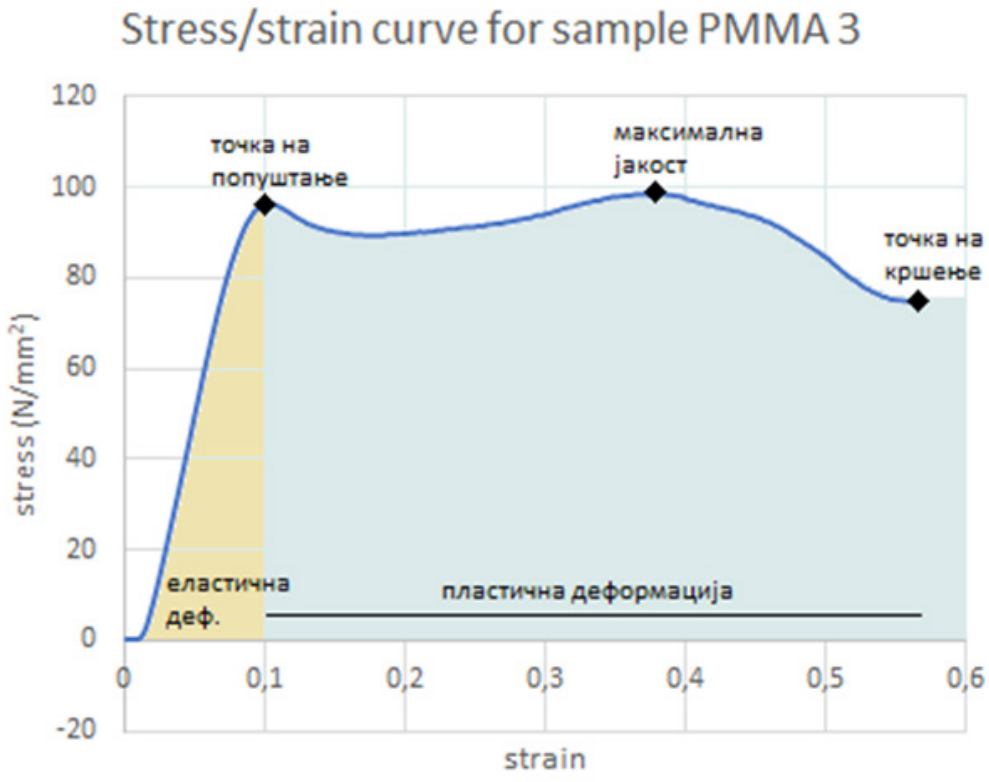
The average density of tested samples is shown in Table 1. All groups had normal distribution, as shown by the Shapiro-Wilk test. A one-way ANOVA revealed no statistically significant difference in density between at least two groups (F=1.831, p = .077), showing the homogeneity of specimen production.

Table 1. Sample density (mg/mm^3)

Group	№ of samples	Average density (mg/mm^3)	SD	Shapiro-Wilk P value
PMMA	8	1.216	0.042	0.993
V 2.5%	8	1.187	0.047	0.246
M 2,5%	8	1.173	0.052	0.551
VM 2.5%	10	1.202	0.017	0.116
VM 5%	8	1.188	0.030	0.517

The stress/strain relationship for sample 3 from PMMA group is presented in the graph in Figure 4 as a typical example of sample behavior. The first part of the graph curve is linear and represents the elastic sample deformation. When the strain of the yield point is reached, the stress begins to decrease and then a significant plastic deformation with a slight stress increase occurs until the sample breaks. The analysis of the compressive strength was performed with the yield point values, as they either coincide with or occur prior to the breaking point.

Figure 4. Stress/strain relationship for sample 3 from PMMA group

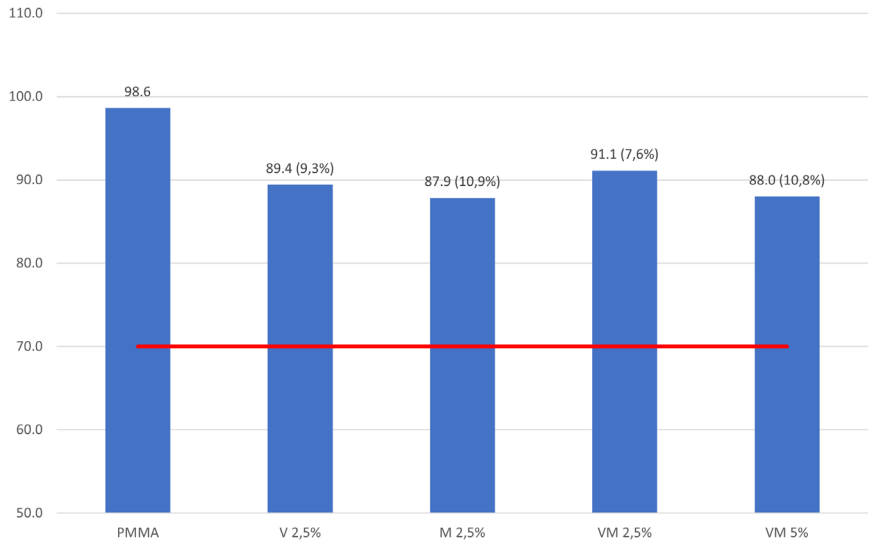


The average compressive strength was significantly above the threshold of 70 MPa in all examined groups (one sample t test, p<0.0001 for all groups). The percentage values above each column in Figure 5 represent the relative decrease in the compressive strength of ALBC groups compared to PMMA.

The Shapiro-Wilk test showed a normal distribution of data across all groups (p>.05 for all groups), and there was homogeneity of variances (Levene's test F=1.575, p=.201).

There were statistically significant differences between group means as determined by one-way ANOVA (F (4.37) = 19.377, p <.0001). Coefficient of determination R^2 was 0.68, suggesting that 68% of the compressive strength variance can be attributed to antibiotic addition.

Figure 5. Average compressive strength of all examined groups. Red line: Minimum acceptable value according to ISO5833



Post hoc comparisons using the Tukey HSD test indicated that the mean score for PMMA was significantly different than that in the groups with added antibiotics. However, no significant differences were observed among ALBC groups (Table 2). The minimum significant difference was 4.7 MPa.

Table 2. Tukey HSD comparisons

Contrast	Difference	Standardized difference	Critical value	p	Significant	Lower bound (95%)	Upper bound (95%)	Lower bound (95%)	Upper bound (95%)
PMMA vs M 2.5%	10.779	7.277	2.867	<0.0001	Yes	6.754	14.804		
PMMA vs VM 5%	10.618	8.520	2.867	<0.0001	Yes	6.593	14.643		
PMMA vs V 2.5%	9.206	5.617	2.867	<0.0001	Yes	5.181	13.230		
PMMA vs VM 2.5%	7.505	5.194	2.867	<0.0001	Yes	3.480	11.530		

VM 2.5% vs M 2.5%	3.274	2.613	2.867	0.158	No	-0.751	7.299		
VM 2.5% vs VM 5%	3.113	3.231	2.867	0.196	No	-0.911	7.138		
VM 2.5% vs V 2.5%	1.701	1.185	2.867	0.745	No	-2.324	5.725		
V 2.5% vs M 2.5%	1.573	1.069	2.867	0.795	No	-2.452	5.598		
V 2.5% vs VM 5%	1.413	1.143	2.867	0.851	No	-2.612	5.437		
VM 5% vs M 2.5%	0.161	0.158	2.867	1.000	No	-3.864	4.185		

q studentized range statistic: 4.054

Minimum significant difference: 4.721

Discussion

PMMA polymerization creates chemical bonds that determine its mechanical properties. Antibiotic molecules do not participate in the polymerization chain reaction; therefore, their presence in the polymer matrix decreases its mechanical performance. *In vitro* studies have shown a significant decrease in the compressive strength of bone cement loaded with cefazoline, cefuroxime, ceftazidime, meropenem, vancomycin, clindamycin and gentamycin, with clindamycin and gentamycin causing decrease below the minimal values necessary for weight bearing.[10]

Double antibiotic loading of bone cement is considered to have multiple benefits. Studies examining bone cement loaded with vancomycin and a second antibiotic showed that the addition of the second antibiotic improved vancomycin release. This is explained by the phenomenon of "passive opportunism", meaning that the release of the first antibiotic creates voids in the cement, which in turn facilitate the release of the second antibiotic.[7,11] Combining two antibiotics broadens the antibacterial spectrum of the ALBC. Numerous studies have investigated ALBC with different antibiotic combinations and found greater efficiency of antibiotic combinations in bacterial growth inhibition and reduction of infection incidence.[12] A study of 848 patients with hip fracture treated with hemiarthroplasty showed significantly lower incidence of deep infections in patients who received bone cement loaded with gentamycin and clindamycin compared to those who received ALBC with gentamycin only.[13] In another study that tested *in vitro* bacterial growth inhibition, ALBC samples containing vancomycin inhibited all Gram-positive bacteria, and when meropenem was added, inhibition of *E. coli* and *P. aeruginosa* was also observed.[14]

In this study, we examined the compressive strength of different antibiotic combinations that could potentially be used for primary and secondary infection prevention in arthroplasty. The compression test evaluates the maximum compressive force before the plastic deformation of cylindric specimens occurs. Compressive strengths of commercially available bone cements differ depending on their brand and composition, and range commonly between 80 and 100 MPa.[15] However,

all commercially available ALBCs must meet the ISO requirement to withstand a compression force of at least 70 MPa.

In our study, all ALBC groups had significantly lower compressive strength compared to antibiotic-free PMMA. All tested groups had an average compressive strength significantly above the threshold of 70 MPa set by the ISO5833. Persson *et al.* also tested ALBC with different doses of vancomycin and meropenem and found no significant decrease in the compressive strength compared to antibiotic-free control, although there was some reduction in the compressive strength in all ALBC groups.[16] The discrepancy with our findings may be attributed to differences in cement and antibiotic brands that may influence some of the variability of the bone cement compressive strength, since we found that only 68% of the compressive strength variability could be attributed to antibiotic addition.

Lilikakis and Sutcliffe tested various cement brands loaded with vancomycin of 2.5% w/w, 5%w/w and 10% w/w. They found that all tested doses caused a significant drop in the compressive strength of all examined brands, with most values being significantly above 70 MPa. Only the 10% w/w dose had a compressive strength of 74.55 MPa, and did not significantly differ from the threshold of 70 MPa.[17] Wang *et al.* found that meropenem can be added to bone cement in doses up to 15% of weight without significantly altering its mechanical properties, while establishing antibiotic release for 24 days at 37°C.[18] According to them, high doses of vancomycin (5%, 10%) lower the compressive strength of bone cement below 70 MPa.

In this study, we did not have the resources to test different cement brands. Although we expect that trends in mechanical properties changes would remain the same across different brands, the magnitude of changes may differ, as shown in the study of Lilikakis and Sutcliffe.[17] Using these antibiotic doses with different cement brands, especially at the highest dose, should be undertaken with caution. Investigation of different brands with the same antibiotic doses may show the magnitude of differences between them and their clinical significance.

In conclusion, meropenem and vancomycin loading decreases the compressive strength of bone cement. However, all tested doses meet the compressive strength requirements set by the international standard. Therefore, they may be considered for use in arthroplasty procedures in high-risk patients, particularly for secondary prevention in patients where infection was caused by susceptible organisms.

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