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Experimental Validation of Antimicrobial Drug Combinations for Bone Cement Impregnation

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Abstract

Background. The implantation of an antimicrobial spacer is widely used in the comprehensive treatment of periprosthetic joint infection (PJI). Most commonly, bone cement is additionally impregnated with vancomycin, which is active only against Gram-positive bacteria. However, there is a global increase in Gram-negative bacterial resistance to most antibiotics, necessitating the development of new approaches to overcome this resistance, including in the context of local antibacterial therapy.

The aim of the study was to determine the duration of antimicrobial activity and the mechanical properties of gentamicin-containing bone cement samples additionally impregnated with the combinations of highly dispersed silver (HD-Ag) and various antibiotics.

Methods. Control samples were prepared using the commercial polymethylmethacrylate-based bone cement DePuy CMW 3 Gentamicin (DePuy Synthes), which contains 4.22% gentamicin. Additionally, six experimental samples with different combinations of antimicrobial agents were prepared and tested. Antimicrobial activity (AMA) was assessed against *S. aureus* (MSSA, MRSA), *K. pneumoniae*, and *P. aeruginosa*. The mechanical properties of the most effective samples were evaluated in comparison with the control samples. Statistical analysis was performed using the Past 4 software system.

Results. The control samples of commercial bone cement demonstrated the shortest duration of activity against MSSA (7 days) and showed no activity against MRSA or Gram-negative bacteria. The addition of 10 wt% fosfomycin and HD-Ag to the bone cement (BC 1) tripled the AMA duration against MSSA, *K. pneumoniae*, and *P. aeruginosa*.The addition of 5 wt% vancomycin to BC 1 (BC 2) extended the AMA duration against Gram-negative bacteria to 14-16 days and against *Staphylococcus* spp. to 4 weeks. The highest activity against Gram-negative bacteria was observed in samples containing HD-Ag and 10 wt% aztreonam (BC 5 and BC 6), whose mechanical properties did not significantly differ from the control samples.

Conclusion. Combinations containing HD-Ag, vancomycin, fosfomycin, and aztreonam demonstrated prolonged antimicrobial activity. This may improve the effectiveness of the debridement stage in two-stage revision arthroplasty for hip periprosthetic joint infection, making these combinations promising for clinical application.

Keywords: periprosthetic joint infection, antimicrobial spacer, highly dispersed silver, bone cement impregnation.

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Экспериментальное обоснование комбинаций антимикробных препаратов для импрегнации костного цемента

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Реферат

Введение. Имплантация антимикробного спейсера широко применяется в комплексном лечении перипротезной инфекции (ППИ). Чаще всего костный цемент дополнительно импрегнируют ванкомицином, который активен только в отношении грамположительных бактерий. Однако во всем мире отмечается рост резистентности грамотрицательных бактерий к большинству антибиотиков, что требует разработки новых подходов для преодоления этой устойчивости, в том числе в случае применения локальной антибактериальной терапии.

Цель исследования — определить длительность антимикробной активности и прочностные свойства образцов гентамицин-содержащего костного цемента, дополнительно импрегнированных комбинациями высокодисперсного серебра (ВД-Ag) с различными антибиотиками.

Материал и методы. Контрольные образцы были изготовлены из коммерческого костного цемента на основе полиметилметакрилата DePuy CMW 3 Gentamicin (DePuy Synthes), содержащего 4,22% гентамицина. Дополнительно были изготовлены и протестированы 6 опытных образцов с добавлением разных комбинаций антибактериальных препаратов. Антимикробную активность (АМА) оценивали в отношении *S. aureus* (MSSA, MRSA), *K. pneumoniae* и *P. aeruginosa*. Прочностные свойства наиболее эффективных образцов оценивали в сравнении с контрольными образцами. Статистический анализ проводили средствами программной системы Past 4.

Результаты. Контрольные образцы из официнального костного цемента продемонстрировали наименьшую продолжительность активности в отношении MSSA (7 дней) и не проявляли активность в отношении MRSA и грамотрицательных бактерий. Добавление 10 масс.% фосфомицина и ВД-Ag в костный цемент (КЦ 1) увеличило продолжительность АМА в отношении MSSA, *K. pneumoniae* и *P. aeruginosa* в три раза. Добавление к КЦ1 5 масс.% ванкомицина (КЦ 2) продлило АМА образцов в отношении грамотрицательных бактерий до 14–16 сут., стафилококков — до 4 нед. Наибольшей активностью в отношении грамотрицательных бактерий обладали образцы с ВД-Ag и 10 масс.% азтреонама (КЦ 5 и КЦ 6), прочностные характеристики которых значимо не отличались от контрольных образцов.

Заключение. Комбинации, содержащие ВД-Ag, ванкомицин, фосфомицин и азтреонам, показали длительную антимикробную активность. Это может улучшить результаты санирующего этапа двухэтапного лечения перипротезной инфекции тазобедренного сустава, что делает их перспективными для клинического применения.

Ключевые слова: перипротезная инфекция, антимикробный спейсер, высокодисперсное серебро, импрегнация костного цемента.

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INTRODUCTION

Periprosthetic joint infection (PJI) remains one of the most relevant and difficult-to-treat complications of arthroplasty. According to the literature, the risk of developing PJI reaches up to 2% after primary arthroplasty, despite advancements in surgical techniques and the use of various treatment methods [1, 2, 3].

Two-stage revision arthroplasty is the treatment of choice for most patients with chronic hip PJI [4]. The main advantage of this method is the implantation of an antimicrobial spacer impregnated with various antibacterial agents, creating a local antibiotic depot during the first stage of treatment. The antimicrobial spacer is made by mixing antimicrobial agents with polymethylmethacrylate (PMMA)-based bone cement, including pre-impregnated with gentamicin [5, 6, 7]. The most common pathogens of PJI are Gram-positive bacteria, particularly *Staphylococcus aureus* and *Staphylococcus epidermidis* [8]. PJI caused by Gram-negative pathogens is considered the most challenging to treat [9, 10]. The primary reason for this is the high resistance of these pathogens to antimicrobial agents [11]. The antimicrobial activity of commercial gentamicin-containing bone cement (BC) without additional antibiotic impregnation lasts only for the first 24 hours, making it essentially ineffective against Gram-negative bacteria [12, 13]. Vancomycin is the most commonly used antibiotic added to BC for the preparation of antimicrobial spacers [14]. However, this antibiotic has a narrow spectrum of action and is effective only against Gram-positive pathogens. Approximately in 10-17% of cases [4, 15], when Gram-negative bacteria are involved in the etiology of PJI, local therapy is ineffective. It is important to note that in recent years, there has been a global increase in the resistance of Gram-negative bacteria to most antibiotics, necessitating the development of new strategies to overcome this resistance, including in the context of local antibacterial therapy [16].

The problem of the short duration of antimicrobial activity in bone cement spacers, despite additional antibiotic impregnation, is widely discussed in scientific literature. It is known that the elution of antibiotics added to the spacer into the infection site at effective concentrations lasts no more than three days after implantation [17]. However, R. Gálvez-López et al. reported prolonged antimicrobial activity of bone cement for up to 30 days when impregnated with a combination of gentamicin, vancomycin, and moxifloxacin [18]. The same study also found a reduction in the elution of meropenem and ertapenem as early as the fourth day, despite their high antimicrobial activity against Gram-negative microorganisms.

The study by R. Krassnig et al. demonstrated that the addition of silver ions to bone cement without additional antibiotic impregnation maintained antimicrobial activity for up to 9 weeks [19]. Additionally, in our previous *in vitro* study, we found that incorporating highly dispersed silver (HD-Ag) into bone cement during the formation of a vancomycin-containing spacer significantly prolonged its antimicrobial activity (up to 34 days). This effectively prevented the formation of microbial biofilms on the surface of the spacer throughout the entire antibiotic release period [20]. These findings suggest that HD-Ag, in combination with agents active against a broad spectrum of pathogens, may further extend the duration of antimicrobial activity in bone cement samples. This hypothesis defined the aim of our study.

The aim of the study was to determine the duration of antimicrobial activity and the mechanical properties of gentamicin-containing bone cement samples additionally impregnated with the combinations of highly dispersed silver (HD-Ag) and various antibiotics.

METHODS

Sample preparation. The samples were prepared using commercial PMMA-based bone cement, DePuy CMW 3 Gentamicin (DePuy Synthes), which contains 4.22% gentamicin. The samples were obtained by mixing 40 g of the dry substance with various combinations of antimicrobial agents, including vancomycin (Kraspharma, Russia), aztreonam (Ruzpharma, Russia), poviargol (Tekhnolog, Russia), meropenem (Kraspharma, Russia), and fosfomycin (Kraspharma, Russia). A total of seven different antimicrobial formulations were included in the experiment (Table 1). The resulting dry mixture was combined with the required amount of methylmethacrylate and molded into samples.

Table 1

Bone cement formulations

	Gentamicin-containing BC	Vancomycin	Fosfomycin	Meropenem	Aztreonam	HD-Ag
B	+					
BC1	+		10 wt%			10 wt%
BC2	+	10 wt%	2.5 wt%			10 wt%
BC3	+	5 wt%		5 wt%		10 wt%
BC4	+			10 wt%		10 wt%
BC5	+				10 wt%	10 wt%
BC6	+	5 wt%			10 wt%	10 wt%

wt% – percentage by weight.

Assessment of antimicrobial activity. To determine the duration of antimicrobial activity (AMA) against the reference strains of Gram-positive and Gram-negative bacteria, standard beads with a 9 mm diameter and 0.4 g weight were prepared. The assessment of AMA duration for the tested samples was conducted following the methodology used in our previous study [21].

Assessment of mechanical strength. The mechanical strength of the bone cement was evaluated at the branch of the Petersburg Nuclear Physics Institute named by B.P. Konstantinov of National Research Centre "Kurchatov Institute" – Institute of High-Molecular Compounds. According to GOST ISO 5833-2011, the cement's ability to withstand loads and external forces was assessed using the following parameters: tensile strength, bending strength, and compression strength, measured in megapascals (MPa) [22].

Test samples for tensile, compression, and bending strength assessments were prepared using metal molds coated with a thin layer of anti-adhesive lubricant based on silicone resin to prevent the adhesion of the polymerized material to the mold. After that the specimens were extracted and cut according to the respective test method:

– bending strength testing – samples with a working section of 30 mm, approximately 5 mm in width and 3 mm in thickness;

– tensile strength testing – dumb-bell specimens with a working section of 25 mm, approximately 4 mm in width and 2 mm in thickness;

– compression strength testing – cylindrical samples with an approximate working height of 10 mm and approximate diameter of 8.5 mm.

The study of the deformation and strength properties of the prepared samples under tensile, bending (using three-point bending clamps), and compression (using compression clamps) loads was conducted at room temperature using a 1958U-10-1 universal testing machine (Russia).

Statistical analysis

The registration, systematization of initial data, and visualization of the obtained results were performed in Microsoft Office Excel spreadsheets. Statistical analysis was conducted using the Past 4 software system. Normality of distribution of quantitative variables was tested using graphical method and showed that the results obtained in determining the strength of the samples corresponded to a normal distribution. For the description of a variable, the mean value and 95% confidence interval (95% CI) were used. Comparison of quantitative variables between groups of samples was performed using the Student's t-test. The differences were considered statistically significant at $p<0.05$.

RESULTS

The study of AMA in bone cement samples revealed that the control samples of commercial gentamicin-containing bone cement exhibited the shortest AMA duration against MSSA (7 days) and no activity against MRSA. The addition of 10 wt% fosfomycin and HD-Ag (BC 1) increased

AMA duration threefold against MSSA, *K. pneumoniae*, and *P. aeruginosa*. However, the effect on MRSA was minimal, lasting only 2 days. Subsequent addition of 5 wt% vancomycin to this composition (BC 2) extended AMA duration against Gram-negative bacteria to 14-16 days and against both *Staphylococcus* strains to 4 weeks.

In an attempt to develop a combination with enhanced activity against Gram-negative pathogens, meropenem was added to the HD-Ag–containing bone cement. However, the resulting samples (BC 3 with 5 wt% meropenem and BC 4 with 10 wt% meropenem) did not exhibit a longer AMA duration compared to BC 2. Doubling the meropenem dose from 5 wt% (BC 3) to 10 wt% (BC 4) also failed to significantly extend AMA against *Staphylococcus* spp. or *P. aeruginosa*, though the duration of activity against *K. pneumoniae* increased from 15 to 25 days.

Bone cement samples containing HD-Ag and 10 wt% aztreonam (BC 5 and BC 6) maintained activity against *K. pneumoniae* for over 280 days, while their activity against *P. aeruginosa* persisted for 2 weeks. It was concluded that the addition of 5 wt% vancomycin (BC 6) prolonged the activity against *Staphylococcus* spp. to 10 days, whereas BC 5 inhibited MSSA growth for only 7 days and had no effect on MRSA.

Thus, the most effective antibiotic combinations for the impregnation of HD-Ag-containing bone cement were: 1) vancomycin (10 wt%) + fosfomycin (2.5 wt%), which provided 4 weeks of activity against *Staphylococcus* spp. and 2 weeks against Gram-negative pathogens; 2) vancomycin (5 wt%) + aztreonam (10 wt%), which exhibited activity against *K. pneumoniae* for over 280 days, *P. aeruginosa* for 2 weeks, and *Staphylococcus* spp. for 10 days. These combinations were selected for further mechanical strength testing (Figure 1).

The evaluation of stress-strain properties demonstrated that the ultimate mechanical strength of bone cement samples decreased with additional antibiotic impregnation, regardless of the type or amount of antimicrobial agent used (Figure 2). During tests, there were no statistically significant differences ($p>0.05$) in compression or bending strength between any of the tested samples, including the control gentamicin-containing commercial cement. However, tensile strength testing revealed a significant reduction in mechanical properties for BC 5 and BC 6, which were additionally impregnated with antimicrobial combinations. Compared to the control samples, the tensile strength of BC 5 decreased by 45.8% ($p<0.005$), while of BC 6 by 53.3% ($p<0.005$).

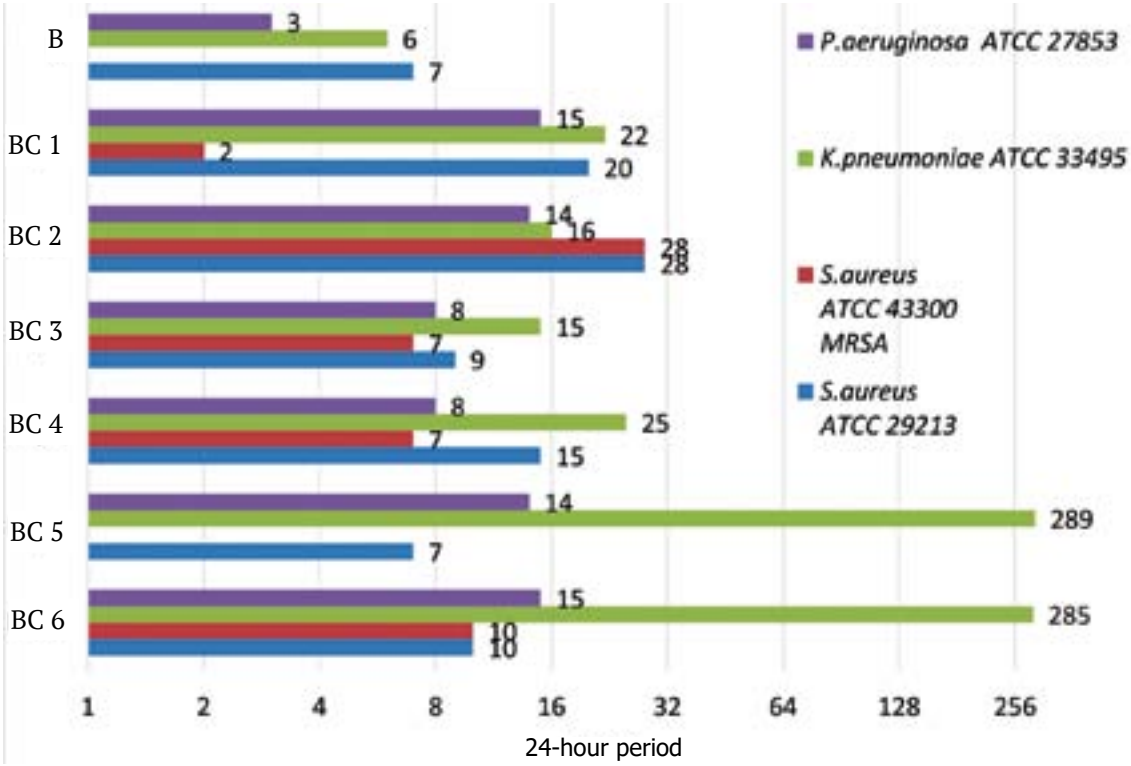

Figure 1. Duration of antimicrobial activity of bone cement samples against reference bacterial strains

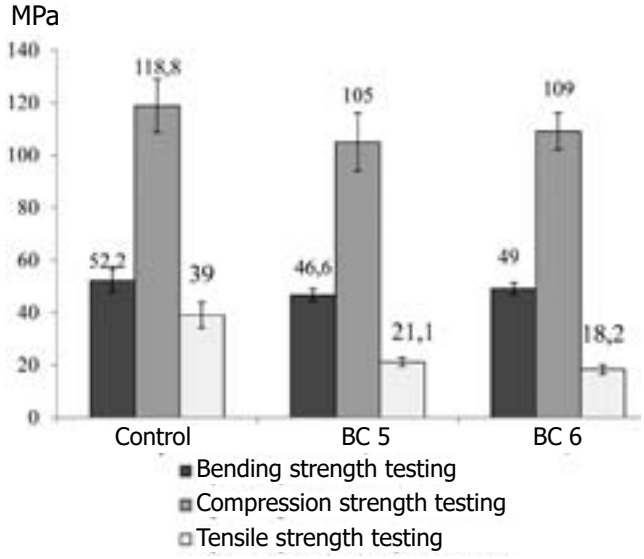

Figure 2. Mechanical properties of bone cement samples

DISCUSSION

It is known that the additional impregnation of bone cement with various antibacterial agents not only determines the duration of antimicrobial activity but also affects its mechanical properties [22, 23]. The addition of two or more antibacterial agents during the mixing of bone cement broadens the spectrum of activity of the antimicrobial spacer and can also result in prolonged drug release [24]. During the debridement stage of the two-stage treatment of PJI, the most commonly used spacer is based on gentamicin-containing cement with the addition of vancomycin [25]. Despite its broad spectrum of activity, gentamicin is less effective against MRSA and Gram-negative bacteria [26]. These facts were confirmed in our study, where the control samples of gentamicin-containing bone cement exhibited no activity against MRSA and suppressed the growth of Gram-negative bacteria for no more than 6 days. Vancomycin is a narrow-spectrum drug that is effective only against Gram-positive pathogens. However, its addition appears to increase the porosity of bone cement, which promotes greater elution of antibiotics, including gentamicin, and consequently, longer activity of BC 1 samples against the tested strains, as we previously demonstrated [12]. Additionally, J.R. Brooks et al. showed that bone cement samples with the addition of vancomycin and another drug from the aminoglycoside group, tobramycin, prevented the formation of *P. aeruginosa* biofilms for up to 5 days [27].

The conducted study showed that the combination of HD-Ag with various antimicrobial agents can alter the antimicrobial activity of the samples against different bacteria. It was found that the most effective combinations for impregnating BC were HD-Ag combined with vancomycin (10 wt%) and fosfomycin (2.5 wt%) (BC 2), as well as with vancomycin (5 wt%) and aztreonam (10 wt%) (BC 6). BC 2 samples demonstrated greater activity against staphylococci (4 weeks) and less activity against Gram-negative pathogens (2 weeks). BC 6 samples exhibited pronounced, long-lasting antimicrobial activity against *K. pneumoniae* (>280 days), *P. aeruginosa* (2 weeks), and were slightly less active against staphylococci (10 days). The results of our *in vitro* study on the effectiveness of aztreonam for bone cement impregnation are consistent with the findings of P.H. Hsieh et al., who analyzed the concentration of aztreonam in the synovial fluid of 46 patients with PJI after the installation of an antimicrobial spacer. The authors demonstrated that the concentration of aztreonam exceeded the minimum inhibitory concentration for 100 days or more, following the implantation of the antimicrobial spacer [28].

In an *in vitro* study, V. Yuenyongviwat et al. found that the duration of antimicrobial activity of bone cement with fosfomycin against MRSA is no more than 3 days [29]. In our earlier *in vitro* study, we demonstrated the prolonged antimicrobial activity of BC samples containing 20 wt% fosfomycin against MSSA and *K. pneumoniae* (28 and 17 days, respectively) and only 5 days against MRSA [12]. The experimental data obtained were confirmed by the clinical and economic effectiveness of using fosfomycin compared to vancomycin for impregnating spacers in the treatment of polymicrobial PJI [30]. The prolonged (up to 28 days) antimicrobial activity of BC 2 samples with fosfomycin against MSSA and MRSA, established in this study, is likely due to its combination with vancomycin and HD-Ag, which increases the porosity of the material itself and ensures the elution of additional antimicrobial agents. The obtained results confirm the effectiveness of the selected combinations of antimicrobial agents, suggesting that they can be considered as an additional therapeutic option

in the combined treatment of patients with PJI, especially in case of polymicrobial infection.

According to GOST ISO 5833-2011, acrylic cements must meet a number of requirements for residual deformation and polymerization: bending strength (at least 50 MPa), bending modulus of elasticity (at least 1800 MPa), and compression strength (at least 70 MPa). Comparing the data obtained from testing the control samples with the values specified in the standard, it can be stated that they meet the requirements of the standard in terms of the average bending strength – 52.2 MPa (95% CI 47.7-56.7) and compressive strength – 118.8 MPa (95% CI 108.7-128.9). The breaking points of samples with additional antimicrobial agents were slightly lower than the standard values for bending strength. The bending strength for BC 5 and BC 6 samples was 46.6 MPa (95% CI 43.3-48.9) and 49 MPa (95% CI 46.8-51.2), respectively. However, no significant differences were found between these values and those of the control samples. Our results are consistent with the experimental study by A.V. Digtiar et al., who showed that the inclusion of 20 wt% antibiotic in bone cement does not significantly reduce its strength limit below the standard set by GOST, with a strength of 119.7 MPa (95% CI 112.1-127.3). However, with the addition of 25 wt% antibiotic, the breaking point decreases by more than twofold and does not meet the GOST standards [31]. Additionally, J.W. Kwong et al. demonstrated that, despite the prolonged antimicrobial activity, the addition of 15 wt% vancomycin to bone cement reduces its stress-strain properties during compression and bending tests [32].

CONCLUSION

Since antimicrobial spacers are temporary implants whose primary function is joint cavity filling and local antibiotic therapy, our findings support the potential use of gentamicin-containing bone cement supplemented with HD-Ag, vancomycin, fosfomycin, or aztreonam for antimicrobial spacer formation. The prolonged antimicrobial activity of the investigated combinations, without the significant deterioration of cement mechanical properties, suggests their effectiveness in treating periprosthetic joint infections caused by Gram-negative microorganisms and polymicrobial infections.

DISCLAIMERS

Author contribution

Bozhkova S.A. — study concept and design, data analysis and interpretation, drafting and editing the manuscript.

Gadzhimagomedov M.Sh. — data acquisition, analysis and interpretation, statistical data processing, drafting the manuscript.

Gordina E.M. — conducting bacteriological studies, statistical data processing, drafting and editing the manuscript.

Antipov A.P. — conducting the experiment, data acquisition, analysis and interpretation, drafting the manuscript.

Vaganov G.V. — conducting the experiment, drafting the manuscript.

Yudin V.E. — conducting the experiment, drafting the manuscript.

All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

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Ethics approval. Not applicable.

Consent for publication. Not required.

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