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Elution of vancomycin and meropenem and their combinations from various bone cement materials

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Abstract

Introduction Saturation of bone defect filling materials with antibacterial agents is used for the treatment of patients with infectious bone complications and for their prevention.

The **purpose** of the work was to evaluate the elution rate of vancomycin and meropenem from bone cements based on polymethyl methacrylate and polyurethane polymers impregnated into the material in their combination.

Materials and methods In an *in vitro* study, a comparative analysis of the kinetics of vancomycin and meropenem release from two materials was performed that were based on polyurethane polymers (PU series) and polymethyl methacrylate (PMMA series). Antibiotics were added to the materials before their polymerization in the following proportions: group 1 — polymer : antibiotic 10 g : 1 g (0.5 g vancomycin + 0.5 g meropenem); group 2 — polymer : antibiotic 10 g : 0.5 g (0.25 g vancomycin + 0.25 g meropenem). Samples loaded with one antibiotic were used as a control: group 1v — polymer : antibiotic 10 g : vancomycin 0.5 g; group 1m — polymer : antibiotic 10 g : meropenem 0.5 g; group 2v — polymer: antibiotic 10 g: vancomycin 0.25 g; group 2m — polymer: antibiotic 10 g: meropenem 0.25 g.

Results Vancomycin elution from both PMMA- and PU-based materials loaded with a vancomycin+meropenem was greater in final volume and longer in time than from materials containing vancomycin alone. Conversely, meropenem release from PMMA and PU loaded with a vancomycin + meropenem mixture was less in volume than from the materials containing meropenem alone.

Discussion The use of a vancomycin-meropenem complex in bone cements reveals the following feature: meropenem promotes the release of vancomycin from the studied materials, while the elution of meropenem itself is reduced.

Conclusion Combining antibiotics for impregnation into materials for bone defect filling has an impact on the kinetics of antibiotics release, unlike the release kinetics of an antibiotic loaded into the material as monotherapy.

Keywords: osteomyelitis, bone defect, bone cement, antibiotics, elution kinetics

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INTRODUCTION

Currently, the effective practice of saturating the materials for filling bone cavities and defects (the so-called bone cement) with various antibiotics is widely used for the prevention and complex treatment of patients with periprosthetic infection and osteomyelitis [1–3]. The principle of this approach is a gradual release of an antibiotic from the material to achieve a more effective local therapeutic concentration of antibiotics than with their parenteral administration, as well as to reduce the toxic effect of antibiotics on the body [4–6]. The technology of using bone cement with antibiotics has proven to be quite effective in primary joint arthroplasty for the prevention of deep infections [7]. Therefore, the addition of antibiotics to bone cements has become a fairly routine practice. The expansion of using this technology in practice is associated with a wide range of different antibiotics [8–10]. An additional stimulus for the development of this field is a prognostically negative situation due to the increase in the number of isolated strains in osteomyelitis, the growth of their resistance to antibiotics, as well as the increase in the proportion of microorganism associations in patients with chronic osteomyelitis [11–13]. The solution to these problems may be associated with both an expansion of the range of materials used to fill in defects [14–16], and with the use of a complex of antibiotics that are tropic to both gram-positive and gram-negative flora [17].

The **purpose** of the work was to evaluate the elution rate of vancomycin and meropenem from bone cement materials based on polymethyl methacrylate and polyurethane polymers that were impregnated alone and in their combination.

MATERIAL AND METHODS

The *in vitro* study compared the kinetics of the release of vancomycin and meropenem (both antibiotics produced by Promomed LLC, Russia) from two materials:

— Rekost, a polyurethane-based polymer material (Nizhny Novgorod, RZN 2014/1646 dated July 3, 2014, unlimited) (PU series);

— bone cement (RU No. FSZ 2012/11622 dated March 19, 2012, unlimited) based on polymethyl methacrylate (PMMA series).

The test materials (according to their instructions for use) were shaped into cylinders 7 mm high and 4 mm wide. Antibiotics were added to the materials before polymerization in the following proportions:

— group 1 — polymer: antibiotic 10 g: 1 g (0.5 g vancomycin + 0.5 g meropenem);

— group 2 — polymer: antibiotic 10g: 0.5g (0.25 g vancomycin + 0.25 g meropenem);

For control, samples loaded with one antibiotic were used:

— group 1v — polymer: antibiotic 10 g: 0.5 g vancomycin;

— group 1m — polymer: antibiotic 10 g: 0.5 g meropenem;

— group 2v — polymer: antibiotic 10 g: 0.25 g vancomycin;

— group 2m — polymer: antibiotic 10 g: 0.25 g meropenem.

The cylinders were incubated in 10 ml of saline in an incubator at 37 °C. The incubation solution (eluate) was changed daily during the first week and once a week thereafter. Six samples were incubated in each group. Samples without antibiotics (zero control) were also incubated in parallel.

In each sample of the incubation solution, the concentration of the tested antibiotics was determined spectrophotometrically against a standard calibration curve using absorbance intensity: vancomycin at 280 nm, meropenem at 298 nm. For calculating the concentrations of the test samples, the extinction values of the zero control samples (without antibiotics) were subtracted. Incubation was stopped when trace amounts of antibiotics were detected in the samples over a two-week period.

The studies were conducted according to the recommendations outlined in GOST ISO 10993-13-2016 "Medical devices. Biological evaluation of medical devices. Part 13. Identification and quantification of degradation products of polymeric medical devices".

The median and interquartile range (Q1–Q3) were calculated in parallel studies. The significance of differences between groups was assessed using the Wilcoxon signed-rank test for independent samples.

The work was carried out *in vitro* without the participation of animals or humans, so the approval of the ethics board was not required.

RESULTS

The dynamics of vancomycin release from PMMA and PU materials impregnated with the vancomycin-meropenem combination in a ratio of 0.5 + 0.5 g (group 1) were virtually identical, with the maximum release of antibiotics after the first day of incubation (Fig. 1). Moreover, the volume of vancomycin released from the PU-based material saturated with the antibiotic complex was higher than from the same material impregnated with vancomycin alone (group 1v). With an antibiotic content of 0.25 + 0.25 g (group 2), vancomycin release was higher in the PMMA series, while vancomycin elution from the PU-based material in group 2v was significantly higher than in group 2.

The release of meropenem from PMMA- and PU-based materials saturated with a vancomycin-meropenem mixture in a ratio of 0.5:0.5 g (group 1) was virtually identical. However, the total volume of meropenem eluted from both materials saturated with the antibiotic mixture was 1.5–2.0 times lower than from the materials loaded with meropenem alone (Fig. 2). In group 2, meropenem release was higher in the PMMA series, while in group 2, it was higher in the PU-based series. Overall, it is worth noting that the volumes of meropenem eluted from both materials containing the antibiotic mixture were significantly lower than from materials loaded with the single drug.

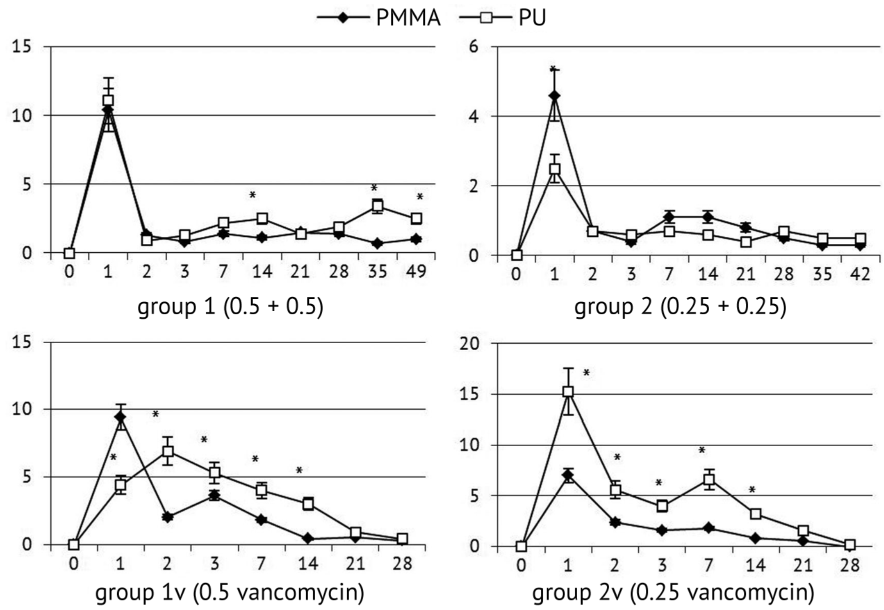

Fig. 1 Dynamics of vancomycin release (% of the total mass of the impregnated antibiotic) from the tested materials (Me, interquartile range); * — significance of differences between series at $p < 0.05$. The abscissa axis shows the day of incubation

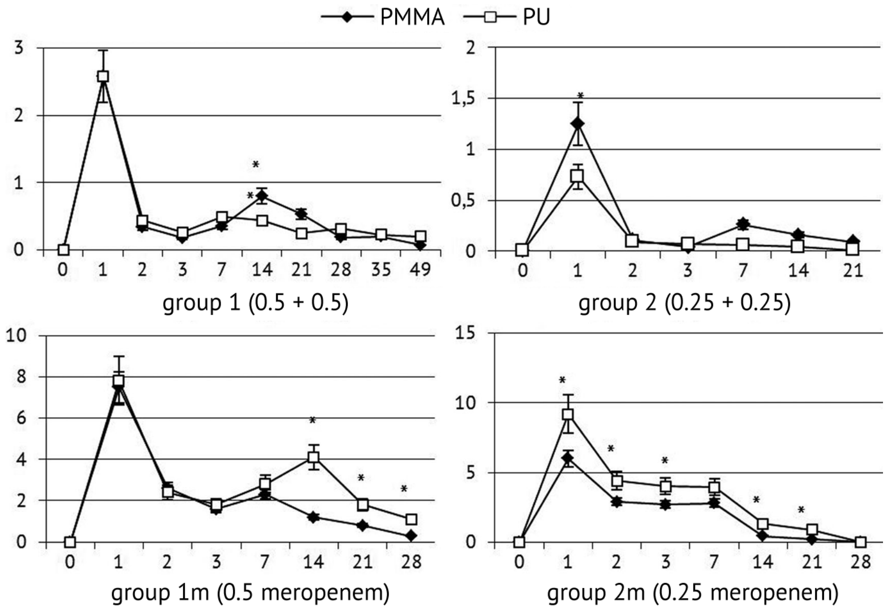

Fig. 2 Dynamics of meropenem release (% of the total mass of the impregnated antibiotic) from the test materials (Me, interquartile range); * — significance of differences between series at $p < 0.05$. The abscissa axis shows the day of incubation

PMMA PU meropenem oup 1m Group 2m

Overall, the overall elution characteristics of vancomycin and meropenem from the tested materials with a mixture of these antibiotics in equal weight ratios differed from the release of them if added in the monovariant (Table 1). Vancomycin elution from both PMMA and PU materials loaded with a vancomycin+meropenem mixture was greater in final volume and lasted longer than from the materials containing vancomycin alone. Conversely, the release of meropenem from PMMA and PU loaded with a vancomycin+meropenem mixture was less in volume than from the materials containing meropenem alone.

Table 1

General results of the release kinetics of antibiotics at different concentrations from PPMA and PU materials (median)

Antibiotic	Group	*L*, days	V_O, %	*Max*, days (%)
		PMMA/PU		
Ванкомицин	1v (mono 0.5)	35/35	20.8/30.1	1(9.4)/1(4.4)
	1 (mixture 0.5)	77/63	45.7#/64.4*#	1(10.4)/1(11.1)
	2v (mono 0.25)	21/21	13.8/33.6*	1(7.0)/1(14.7)
	2 (mixture 0.25)	42/42	42.0#/32.9	1(18.3)/1(10.0)
Меропенем	1m (mono 0.5)	28/28	16.5/21.5	1(7.5)/1(7.7)
	1 (mixture 0.5)	56/56	11.6#/12.5#	1(5.2)/1(5,2)
	2 m (mono 0.25)	14/14	15.3/23.4	1(5,9)/1(9,1)
	2 (mixture 0.25)	21/14	8.1#/4.0*#	1(5.0)/1(2.9)

Note: *L* — duration of antibiotic release; V_O — total volume of released antibiotic in % relative the impregnated total volume; *Max* — term of observation (days) when the maximum release was noted and it percentage (in brackets) relative the total of impregnated antibiotics; * — differences between PMMA and PU significant at $p < 0.05$; # — significant differences from the group of monotherapy at $p < 0.05$

DISCUSSION

The results of this study demonstrate that the release kinetics of vancomycin and meropenem that are loaded into post-osteomyelitic defect filling materials and added as their mixture in an equal weight ratio differed from the release kinetics if the material was loaded with a single antibiotic. Specifically, vanocomycin release from both studied materials loaded as a vancomycin + meropenem mixture was greater than from the materials containing vancomycin alone. Vancomycin release from the PU-based material was more effective than from the PMMA-based material. Conversely, meropenem release from both studied materials loaded as a vancomycin + meropenem mixture was less effective than from the materials loaded with meropenem alone.

Existing literature data are primarily devoted to the elution of antibiotic monopreparations impregnated in PMMA-based bone cement [8–10]. We found only one study that examined the elution of the antibiotic mixture we studied. It was noted that the elution of vancomycin from acrylic cement was independent of the presence of meropenem [18]. Those results are similar to our data, so it can be concluded that the use of a vancomycin-meropenem combination in bone cements exhibits the following feature: one antibiotic (meropenem) promotes the release of the other (vancomycin), while the elution of meropenem itself is reduced.

In general, almost all similar studies of the kinetics of the release of various combinations of antibiotics added to bone cements note a common rule: a combination of antibiotics in materials for filling infected bone defects changes the release characteristics of all the antibacterial components included in the composition, both enhancing and weakening their elution [19, 20]. It was shown that a synergistic effect is observed with a combination of gentamicin and vancomycin: the elution of both antibiotics increases when loaded together into bone cement [21]. With a combination of tobramycin and vancomycin, the release of vancomycin increases compared to the release of vancomycin in its pure form [22]. Enhancement/weakening of the elution of several antibiotics were also described for combinations consisting of three antibiotics (cefazolin, gentamicin, vancomycin) [23].

The dose-dependent features of antibiotic elution according to the results of our study are as follows: for both materials used, a direct relationship was observed between the initial concentration of impregnated antibiotics and the volumes of their elution; thereby the dose/elution relationship was nonlinear, which is also consistent with literature data [24].

The kinetics of antibiotic release depending on the initial mass ratio of the combined antibiotics in the cement has been poorly studied, although the general pattern remains the same here: an increase in the proportion of a single antibiotic can change (increase or decrease) the kinetic profile of another antibiotic [25].

Moreover, the kinetics of antibiotic elution, as shown by our studies and literature data, can be influenced by the composition of the material used to fill bone defects [26, 27] and its viscosity [28].

Therefore, in general, it can be concluded that each antibiotic combination and each cement brand exhibits a unique antibiotic release profile [24]. These circumstances significantly complicate the selection of material and antibiotic combination in practice. Considering that the antibiotic kinetic profile is also determined by the cement composition, the choice of material and antibiotics used in real-life practice can present significant challenges and carry significant risks that the antibacterial efficacy of antibiotic-impregnated bone cements for the management of post-osteomyelitic defects will be lower than expected. Therefore, at this stage, the most feasible approach is to test a bone cement sample with antibiotics for efficacy parameters (elution and antibacterial sensitivity) in an *in vitro* study before clinical use to ensure that the antibiotic combination is suitable for the selected cement [24].

To increase the elution of antibiotics from bone cements, approaches associated with additional modification of the material through its chemical modification, the use of various reinforcing elements, and saturation of the material with antimicrobial drugs that are not antibiotics can be used [29–32].

CONCLUSION

Mixing several antibiotics impregnated in the materials for bone defect repair, such as those based on polymethyl methacrylate and polyurethane polymers, has an impact on the rate of antibiotic elution, as opposed to the release rate of the antibiotic if loaded into the material alone. Specifically, meropenem combined with vancomycin increases the rate of vancomycin release.

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