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Release of antibiotics from the materials for post-osteomyelitic bone defect filling

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Abstract

Introduction The search for materials for bone defect filling that would provide a release of antibiotics in therapeutic levels over a long period is a pressing issue in the treatment of patients with osteomyelitis.

The **purpose** of the work was to compare the kinetics of antibiotic release from materials based on polyurethane polymers for filling post-osteomyelitic bone defects.

Materials and methods A comparative *in vitro* analysis of the kinetic release of cefotaxime, vancomycin, and meropenem from two materials was performed: one was based on polyurethane polymers (RK series) and the other on polymethyl methacrylate (PMMA series). In each series, antibiotics were added to the original materials in three proportions: polymer/ antibiotic — 10:1 (group 1); 10:0.5 (group 2), and 10:0.25 (group 3). The samples were incubated in 10 ml of saline at 37 °C. The incubation solution was changed daily during the first week, and then once a week. Six samples were incubated in each group.

Results It was revealed that the volume of eluted cefotaxime in the PMMA series was higher than in the RK series for all antibiotic concentrations. In turn, for vancomycin and meropenem, it was observed only for group 1 samples. For groups 0.5 and 0.25, a larger volume of released antibiotics was noted in the RK series than in the PMMA series. It was found that in the RK series, the release of vancomycin and cefotaxime in an effective (therapeutic) concentration was more prolonged. In the RK series, there was prolonged release of effective concentrations but in a smaller volume of released antibiotic than in the PMMA series.

Discussion Each material showed its own antibiotic elution profile and each of them may have its own indications. The RK-based material has advantages in terms of the duration of antibiotic elution in therapeutic doses.

Conclusion The release of the studied antibiotics in effective concentrations from the material based on polyurethane polymers is longer than from the PMMA-based material.

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

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INTRODUCTION

Currently, various materials impregnated with antibiotics are widely used to fill in bone defects formed after removal of osteomyelitic foci [1, 2]. This allows for the most effective suppression of the local infectious process, thereby decreasing dependence on systemic antibiotics [3–5]. The main material used for these purposes is polymethyl methacrylate (PMMA) (the so-called bone cement) [6]. The experience of using PMMA as an antibiotic carrier revealed a number of shortcomings in solving the problems of osteomyelitis arrest. In particular, the key shortcoming is the kinetics of antibiotic release from the material as most of it is released within the first day after implantation. Thus, the risk of reinfection may arise in the later period and also there is a toxic load on the patient's organism. An additional negative factor is the difficulty of removing this material [7, 8]. These circumstances support the relevance of searching the main material (carrier) for filling bone defects, which would provide release of antibiotics in therapeutic volumes over a long period [9–11]. In this regard, the domestically developed material *Rekost* (RZN 2014/1646, state registration date 03.07.2014, indefinite) [12] based on polyurethane polymers [13] seems a promising material for solving such problems.

The **purpose** of the work was to compare the kinetics of antibiotic release from materials based on polyurethane polymers for filling post-osteomyelitic bone defects.

MATERIALS AND METHODS

The study is an *in vitro* comparative analysis of the kinetics of release of three antibiotics (cefotaxime, vancomycin, meropenem) from two materials: *Rekost* (RK) based on polyurethane polymers (Nizhny Novgorod, RZN 2014/1646 dated 03.07.2014, indefinitely) (series RK) and bone cement (RU No FSZ 2012/11622 dated 19.03.2012, indefinitely) based on polymethyl methacrylate (series PMMA).

The tested materials (according to the instructions) were used in the shape of cylinders, 7 mm high and 4 mm in diameter. Antibiotics were added to the initial material in three proportions:

1) polymer/ antibiotic — 10:1 (group 1 in each series);

2) polymer/ antibiotic — 10:0.5 (group 0.5 in each series);

3) polymer/ antibiotic — 10:0.25 (group 0.25 in each series).

The cylinders were incubated in 10 ml of physiological solution at 37 °C. The incubation solution was changed daily during the first week, and then once a week. Six samples were incubated in each group. Samples without antibiotics were also incubated (control).

In each sample of the incubation solution, the concentration of the tested antibiotics was determined spectrophotometrically relative to the standard calibration curve by absorption intensity: cefotaxime at 243 nm, vancomycin at 280 nm, meropenem at 298 nm. For calculating the concentration of the experimental samples, the extinction values in the samples of the control material (without antibiotics) were subtracted. Incubation was stopped when trace amounts were noted in the samples over two weeks.

In parallel, the median and interquartile ranges were calculated. The reliability of differences between the groups was assessed using the Wilcoxon W-test for independent samples.

The studies were carried out considering the recommendations specified in GOST ISO 10993-13-2016 "Medical devices. Evaluation of the biological effect of medical devices. Part 13. Identification and quantification of degradation products of polymeric medical devices."

The work was carried out in the format of an *in vitro* study without the use of biomaterials, so an ethical approval was not required.

RESULTS

The results of the cefotaxime release kinetics showed that the antibiotic released from the PMMA series samples was maximal during the first day of the experiment for all concentrations: 25–40 % (Fig. 1). The cefotaxime release from the RK series samples during this period was about 10 %. In subsequent observation periods, the antibiotic release from the RK series samples was, on average, higher than in the PMMA series.

In the PMMA series, the release of vancomycin in the first day of the experiment was also maximal for all concentrations during the entire observation period and significantly exceeded the values of the RK series (Fig. 2). However, in subsequent periods of the experiment, the antibiotic release from the RK series samples was more significant relative to the PMMA series, especially in the 0.25 group.

The release of meropenem in the first day of the experiment in the PMMA series of group 1 was significantly higher than the values of the similar RK series (Fig. 3). In the 0.5 group, the release kinetics in the RK series during the first week of the experiment was identical to that in the PMMA series, and in subsequent periods it even exceeded the release level in the PMMA series. In the 0.25 group, the antibiotic release from the RK series samples was higher relative to the PMMA series at all observation time-points.

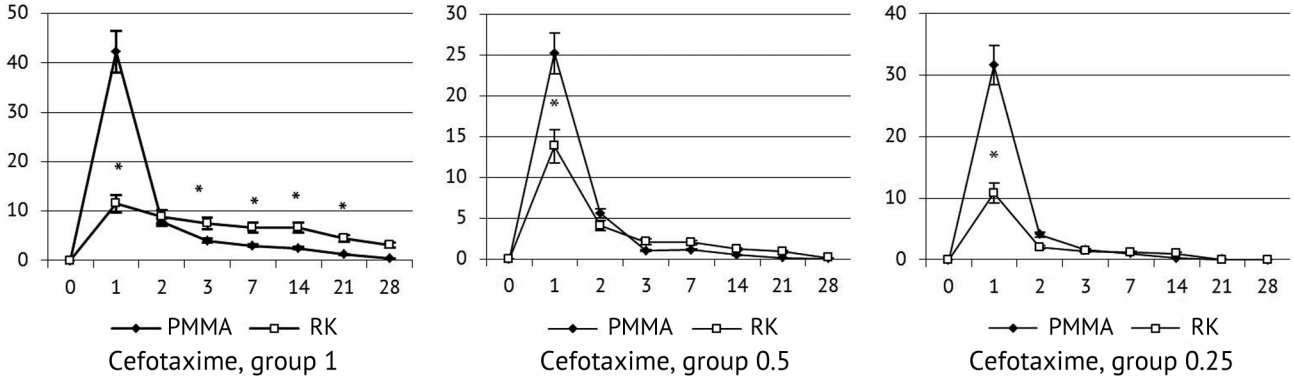

Fig. 1 Dynamics of cefotaxime release (% of the total of the impregnated antibiotic) from the tested materials (Me, interquartile range). * — reliability of differences between series at $p < 0.05$. On the abscissa axis — day of incubation

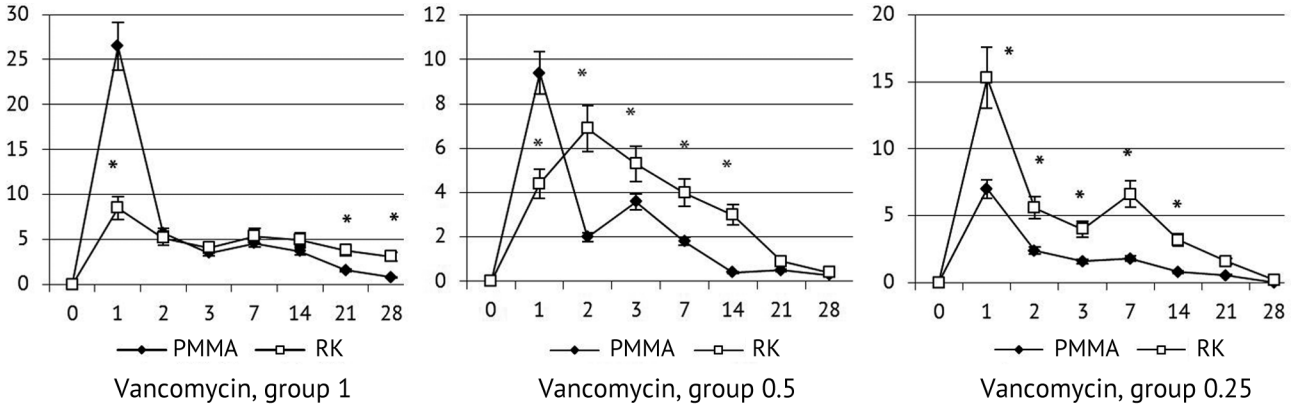

Fig. 2 Dynamics of vancomycin release (% of the total of the impregnated antibiotic) from the tested materials (Me, interquartile range). * — reliability of differences between series at $p < 0.05$. On the abscissa axis — day of incubation

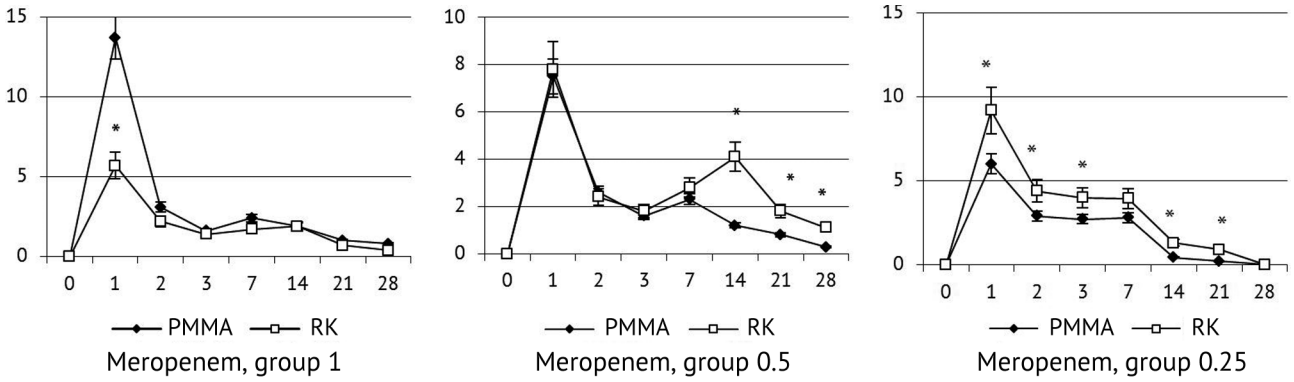

Fig. 3 Dynamics of meropenem release (% of the total of the impregnated antibiotic) from the tested materials (Me, interquartile range). * — reliability of differences between series at $p < 0.05$. On the abscissa axis — day of incubation

The summarized results of the release kinetics of the studied antibiotics in different concentrations from PPMA and RK materials are shown in Table 1. It was found that the total duration of antibiotic release (L) decreased with a decrease in their content in the samples. The total duration of vancomycin and meropenem release was the same for the PMMA and RK groups. For cefotaxime in groups 1 and 0.5, the antibiotic was released from the RK series material for a longer time. However, the total volume (Vo,) of cefotaxime released from PMMA was higher than from RK at all concentrations. For vancomycin and meropenem, the total release from PMMA was in group 1, while in groups 0.5 and group 0.25, a larger volume was released from the RK series material. For all series, the maximum released volume of antibiotics (Max) was noted after the first day of incubation.

Table 1

General results of the kinetics of antibiotic release in different concentrations from PPMA and RK materials (Median)

Antibiotic	Group	L, days PMMA/RK	V_O, % PMMA/RK	Max, days (%) PMMA/RK
Cefotaxime	1	56/70	69.2/48.2	1(52.2)/1(11.5)
	0.5	21/28	30.6/25.5	1(25.2)/1(13.8)
	0.25	14/14	39.7/15.8	1(31.6)/1(10.8)
Vancomycin	1	42/42	52.1/49.5	1(26.5)/1(8.5)
	0.5	35/35	20.8/30.1	1(9.4)/1(4.4)
	0.25	21/21	13.8/33.6	1(7.0)/1(14.7)
Meropenem	1	42/42	25.8/14.3	1(13.7)/1(5.7)
	0.5	28/28	16.5/21.5	1(7.5)/1(7.7)
	0.25	14/14	15.3/23.4	1(5.9)/1(9.1)

Notes: L — duration of antibiotic release; Vo — total volume of released antibiotic (%) relative to the total of the impregnated antibiotic; Max — observation term (days) of maximum volume of the released antibiotic and (brackets) the percentage of this released antibiotic relative to the total impregnated antibiotic

Thus, we have shown that the volumes of released antibiotics depend both on their concentration in the material and on the nature of the material itself. To assess the probable clinical applications of the findings obtained, we compared the amounts of eluted antibiotic with the values of minimum inhibitory concentration (MIC) for the main classes of microorganisms. The MIC values are taken from the "European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for the interpretation of MIC values and zone diameters of inhibition. Version 13.0, 2023" (https://amrnet.crie.ru/upload/iblock/4c9/od4c56ltfmoaatnvk6d8i1n1r4mg1cj8/v_13.0_Breakpoint_Tables_RU_Translation.pdf). According to the references for cefotaxime and meroponem in relation

to *Staphylococcus spp*. the MIC is 4 mg/L, for vancomycin relative to *Staphylococcus spp*. — 2 mg/L, in relation to *Enterococcus spp*. — 4 mg/L, for meroponem relative to *Pseudomonas spp*. — 2 mg/L.

Table 2

Terms of maintaining the level of antibiotics above the MIC values for different microorganisms in eluates from the studied materials

Antibiotic	Groups	*Staphylococcus spp.*, PMMA/RK	*Enterococcus spp.*, PMMA/RK	*Pseudomonas spp.*, PMMA/RK
Cefotaxime	1	7/56	–	–
	0.5	3/7	–	–
	0.25	2/1	–	–
Vancomycin	1	35/42	14/42	–
	0.5	3/21	1/7	–
	0.25	3/14	1/7	–
Meropenem	1	14/14	–	35/21
	0.5	2/2	–	14/21
	0.25	1/1	–	7/7

It was found that the concentration of cefotaxime exceeding the MIC for *Staphylococcus spp*. in the eluate from the RK series samples was maintained longer than for the PMMA series samples in groups 1 and 0.5, lasting 56 and 7 days, respectively (Table 2). In the 0.25 group samples, the concentration of cefotaxime exceeding the MIC was observed in the eluate only during the first two days of incubation in the PMMA series and the first day in the RK series. The concentration of vancomycin in the eluate higher than the MIC for *Staphylococcus spp*. and *Enterococcus spp*. from the samples in the RK series was maintained longer than in the PMMA series in all studied groups. The concentration of meropenem was higher than the MIC in relation to *Staphylococcus spp*. in the eluate from the RK and PMMC series samples was maintained for the same period. In relation to *Pseudomonas spp*. the MIC was higher in the RK series samples in groups 1 and 0.5 and was maintained longer compared to the PMMA series.

DISCUSSION

The findings allow us to conclude that the volumes of released antibiotics and, accordingly, the duration of maintaining the MIC in the eluates are determined by their concentration in the original material and the type of the carrier. It was shown that the volume of eluted cefotaxime from the PMMA series material was higher than that from the RK series material at all antibiotic concentrations. In turn, for vancomycin and meropenem, this was observed only for samples in group 1. For group 0.5 and group 0.25, a larger volume of released antibiotics was noted in the RK series than in the PMMA series. Assessing such an important parameter as the duration of maintaining the antibiotic level in the eluates above the MIC values, it became obvious that in the RK series, the release of vancomycin and cefotaxime in an effective (therapeutic) concentration was more prolonged. Moreover, an additional criterion in favor of RK is the fact that prolonged maintenance of effective concentrations occurred in smaller volumes of released antibiotic, which reduces the toxic load.

Our findings for the PMMA series are in good agreement with the data reported by other authors [14]. However, the elution indices of the carriers proposed as analogues of PMMA differ significantly. Thus, the antibiotic delivery systems being under development, where calcium phosphate materials act as carriers, have quite variable characteristics in terms of elution duration. In particular, by varying the composition of this material, researchers achieve the duration of antibiotic release in therapeutic volumes (above the MIC values) from one [15] to 18–34 days [16, 17].

The use of artificial polymers, in particular polylactic and polyglycolic acid copolymer (PLGA) as a carrier, appears quite promising due to the fact that the material is degradable, has sufficient mechanical strength and can be used to create 3D models of the defect [18]. However, the available studies demonstrate that the release of antibiotics from this material occurs mainly within the first two days [19, 20].

In terms of biodegradability, it is worth noting the materials of natural origin. Thus, almost a complete release of clindamycin or gentamicin from a hydrogel of human collagen occurred within 18 hours [21]. The use of chitosan as a carrier increases the duration of elution, but its speed depended on the nature of the antibiotic: cefotaxime released within 3 days, gentamicin and lincomycin within 15 days [22].

Attempts to increase the duration of antibiotic elution in therapeutic doses led researchers to develop materials of combined composition. Thus, the material based on collagen and hydroxyapatite showed vancomycin elution within 28 days [23], ciprofloxacin elution from a hydrogel based on carboxymethyl-resistant starch and polyacrylic acid released for 3 days [24], ampicillin elution from chitosan/starch nanocomposites occurred within 24 hours [25].

New potential carriers are also being developed: nanocomposite hydrogels from polyacrylamide/dextran containing carbon quantum dots [26], hydrogels based on aspartic acid/acrylamide [27], ion-containing carriers [28], molecularly imprinted polymers, which are synthetic receptors [29].

In general, the majority of current studies are the works in which an attempt to obtain materials with characteristics of prolonged release of antibiotics was the search for optimal chemical compositions. Therefore, a group of new materials that allow regulation of release kinetics by changing the physicochemical parameters of the carrier looks quite interesting. Thus, a group of authors demonstrated the possibility of regulating the rate of antibiotic elution from oxide nanotubes by modifying the sizes of those nanotubes [30]. Carriers have been proposed in which the release of antibiotics is regulated by an alternating magnetic field [31]. A hydrogel has been developed, the rate of release of antibiotics from which depends on the pH of the medium and the presence of free radicals in it [32].

The presented above shows that each material has its own antibiotic elution profile and each of them may have its own indications related to the need for either prolonged elution of the active substance (chronic process) or, conversely, the need to create a "shock" concentration in a local volume (acute process). However, most of the materials used and being developed have limitations on the duration of antibiotic elution in effective concentrations. In this regard, it can be stated that the RK-based material has advantages in terms of the duration of antibiotic elution in therapeutic doses. According to this criterion, RK corresponds to similar materials being developed that are based on calcium phosphate.

In general, based on the study, the RK material appears quite promising as a carrier of antibiotics in the management of bone defects. Moreover, the possibility of achieving a dose of the released antibiotic higher than the MIC values at lower concentrations of drugs in the material will allow impregnating several active drugs into the material to increase the effectiveness of antibiotic therapy. Such studies are available in the literature [33].

Undoubtedly, the design of our study has limitations. In particular, the model of the experiments conducted should be confirmed by further studies on living objects.

CONCLUSION

Thus, the duration of release of studied antibiotics in effective concentrations from the material based on polyurethane polymers is longer than from the material based on PMMA. These characteristics of the studied product seem promising for prevention of infection in management of post-osteomyelitic bone defects.

Conflict of interests *None.*

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