PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 70 (2016), No. 4 (703), pp. 220–226.
DOI: 10.1515/prolas-2016-0035

ANTIBACTERIAL EFFICIENCY OF HYDROXYAPATITE BIOMATERIALS WITH BIODEGRADABLE POLYLACTIC ACID AND POLYCAPROLACTONE POLYMERS SATURATED WITH ANTIBIOTICS

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Infections continue to spread in all fields of medicine, and especially in the field of implant biomaterial surgery, and not only during the surgery, but also after surgery. Reducing the adhesion of bacteria could decrease the possibility of biomaterial-associated infections. Bacterial adhesion could be reduced by local antibiotic release from the biomaterial. In this in vitro *study, hydroxyapatite biomaterials with antibiotics and biodegradable polymers were tested for their ability to reduce bacteria adhesion and biofilm development. This study examined the antibacterial efficiency of hydroxyapatite biomaterials with antibiotics and biodegradable polymers against* Staphylococcus epidermidis *and* Pseudomonas aeruginosa*. The study found that hydroxyapatite biomaterials with antibiotics and biodegradable polymers show longer antibacterial properties than hydroxyapatite biomaterials with antibiotics against both bacterial cultures. Therefore, the results of this study demonstrated that biomaterials that are coated with biodegradable polymers release antibiotics from biomaterial samples for a longer period of time and may be useful for reducing bacterial adhesion on orthopedic implants.*

Key words: S. epidermidis*,* P. aeruginosa*, antimicrobial agents, composite materials, biodegradable polymers.*

INTRODUCTION

The microorganism's ability to infect and colonise implanted biomaterial or some other medical device still remains as a risk factor in the development of nosocomial infections. There have been many recent studies that examine the risk of microbial contamination of biomaterials (Hetrick *et al*., 2006). Infections continue to spread in all fields of medicine related to the implantation of biomaterials. One of the major obstacles against wider use of biomaterial implants is the capacity of bacteria to attach to biomaterial surfaces, which can cause infections associated with biomaterials (Yuehuei *et al*., 1998).

Major pathogens of implant-related infections are staphylococci (*Staphylococcus aureus* and coagulase-negative staphylococci, such as *S. epidermidis*), which are aetiology agents in 25% of all implant infections (McCann *et al*., 2008; Hodgson *et al*., 2014).

S. epidermidis has become the leading pathogen of nosocomial infections. The infection usually develops after joint replacement surgery, central venous catheter implantations and artificial heart valve operations. *S. epidermidis* has a Gram-positive cell wall structure. It is a non-motile and non-spore forming bacteria, which can be easily recognized by microscopic examination, as they form spherical cell clusters resembling bunches of grapes (Kiedrowski *et al*., 2011). Coagulase-negative *Staphylococcus* are among the most frequently isolated bacteria in clinical microbiology laboratories. Bacteria are part of the normal human skin and mucous membrane microflora, and therefore one of the most important tasks of daily diagnostic work is to distinguish clinically significant coagulase-negative *Staphylococcus* infection from the normal microflora (von Eiff *et al*., 2002). *S. epidermidis* belongs to the normal microflora of the skin and mucous membrane. It has the unique and specific property of biofilm formation on implanted biomaterials. The ability of *S. epidermidis* to colonise and build

biofilms on biomaterial implants depends on composition and surface properties of the biomaterial, as well as the ability to produce micro-adhesins (O'Gara *et al*., 2001; Christner *et al*., 2010).

Many studies have shown that the *S. epidermidis* biofilm formation process consists of two phases, defined by biochemical and molecular-cellular levels. In the first phase, the biochemical level, bacterial extracellular polysaccharide adhesins play a primary role in initial bacterial adhesion and mutual adhesion of bacteria (Agarwal *et al*., 2010).

Gram-negative pathogens such as *Pseudomonas aeruginosa* are the second most important aetiological agents in implant-related infections (Peel *et al*., 2012). They can cause life-threatening nosocomial infections, particularly for immunocompromised patients and burn patients (Pruitt *et al*., 1998; Cunha, 2001). The bacterium is widely present in the external environment — soil, water, and in the hospital environment. High antibacterial resistance and the ability to produce a biofilm on artificial surfaces makes bacterial infections difficult to treat and deadly to the patient (Hoiby *et al*., 2001; Drenkard, 2003). *P. aeruginosa* biofilms are formed in five phases, starting with free plankton cell adhesion to the surface, followed by microcolony formation, and finally the dispersion. *Paeruginosa* biofilm is composed of a mixture of polysaccharides, nucleic acids and proteins (Harmsen *et al*., 2007).

The role of other microorganisms such as enterococci, streptococci, and fungi in implant related infections has also been proven. About 40% of cases of infection by *Propionibacterium acnes* (member of the skin deep microflora) are associated with shoulder joint prosthesis infections (Zeller *et al*., 2007; Sampedro *et al*., 2009).

To avoid the risk of postoperative infections and in order to prevent bacterial biofilm development on biomaterials, the optimal solution is the use of antibiotics. Biomaterials with local antibiotic release are being used increasingly nowadays, because they have significant advantages over systemic use of antibiotics (Grainger *et al*., 2013). Systemic antibiotic therapy has several disadvantages: low bioavailability, poor penetration in bacterial infection areas and antibiotic side effects, and ability of bacteria to develop resistance to antibiotics (Pritchard *et al*., 2013).

Polymer particles, including nanoparticles and microparticles created from natural and synthetic polymers have demonstrated several advantages. Polymers can be connected to antibiotics and the biomaterial surface creating high antibacterial stability *in vitro* and *in vivo*, good biological compatibility and multi-functionality. Good potential efficiency is predicted for biomaterials with surfaces with antibiotics immobilized with polymer, which provide steady, sustained release of antibiotics from the implant into tissues. This results in good efficiency in controlling biofilm-producing bacteria. Among the various biodegradable polymers, poly(L-lactic acid) (PLLA) and polycaprolactone (PCL) are widely used in various industries, as they can be derived from renewable resources. PLLA is widely used in surgical implants, biodegradable floss and tissue culture (Armentano *et al*., 2010). The aim of this study was to determine the antibacterial efficiency of hydroxyapatite biomaterials with biodegradable polymers and antibiotics.

MATERIALS AND METHODS

Hydroxyapatite composite material HAp/PLLA+cipro, HAp/PLLA+genta. Hydroxyapatite (HAp) powder was prepared by wet chemical precipitation synthesis from calcium oxide (CaO, Fluka, ≥97 %) and ortophosphoric acid (Sigma-Aldrich, ≥ 85%) solution (Sokolova *et al*., 2014). The obtained as-synthesized powders were uniaxially pressed into pellets (d = 10, H = 3 mm). All samples were sintered at 1100 °C for 1 hour.

To load drugs in the HAp scaffolds, gentamicin (genta) or ciprofloxacin (cipro) was dissolved in deionised water at concentrations of 40 mg/ml of genta and 100 mg/10 ml of cipro. The scaffolds were impregnated with the aqueous drug solution at room temperature, followed by drying at 37 °C. Part of the prepared samples were coated with PLLA.

We prepared solutions of 10 wt% PLLA (Nature Works LLC, Mw = 110 kDa) in dichlormethane (DCM) (Sigma-Aldrich, UK) in order to coat the prepared HAp scaffolds with polymers. PLLA was dissolved in DCM by stirring for 2 h at room temperature. Polymer solution was infiltrated in HAp bioceramic scaffolds using the vacuum impregnation technique at 500 mbar pressure for 15 min. The coated scaffolds were dried at room temperature for 24 h.

The open (P_0) porosity and total (P_t) porosity of scaffolds was determined by the Archimedes method based on the principle that buoyant force is equal to the weight of the fluid displaced (Locs *et al*., 2013).

Observations of the microstructure of coated scaffold cross-sections by scanning electron microscope (SEM) showed that HAp/PLLA scaffolds coated with 10 wt% of PLLA exhibited a porous microstructure with pore size estimated to be in the range of 200 nm to 500 nm (Fig. 1.).

Calcium deficient composite materials CDHAp/PCL+cipro, CDHAp/PCL+genta, CDHAp/PLLA+cipro CDHAp/ PLLA+genta. Calcium deficient hydroxyapatite (CDHAp) powders were synthesised via wet precipitation reaction using the following reactants: calcium oxide (CaO, Fluka, from marble, ≥97%) and orthophosphoric acid (H3PO4, Sigma-Aldrich, ≥85%) and deionised water. Multiple factors were evaluated for effect on product phase composition: e.g., suspension temperature, pH level, acid addition rate and mixing (Sokolova *et al*., 2014).

PCL, PLLA, and CDHAp composites with a range of biopolymer content (20 wt% and 30 wt%) were manufactured using modified novel liquid/solid suspension technology. Genta was dissolved in deionised water to a concentration of 40 mg/ml. Cipro was dissolved in deionised water to a

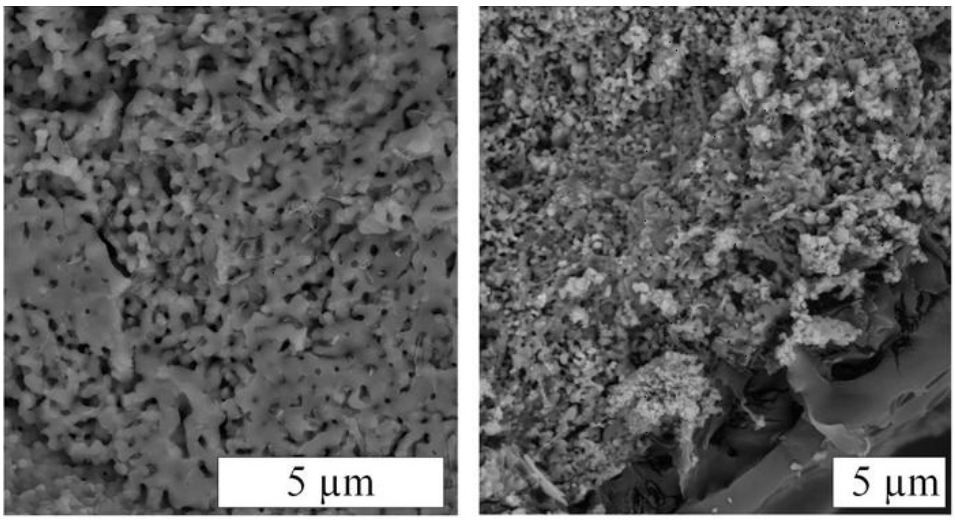

Fig. 1. SEM micrographs of cross-section of HAp/PLLA coated scaffold A – pore diameter in the range of 200 nm to 500 nm, B – PLLA coating (2–5 μm thick).

concentration of 100 mg/10 ml. Predetermined amounts of the solution were mixed with different CDHAp/PCL and CDHAp/PLLA powders to yield 6 wt% genta or cipro in final composition. The obtained powder blends were dried at room temperature for 24 h. The obtained composite material was uniaxially and isostatically pressed into pellets (d = 12.5 mm, H = 2.2 mm).

The porosity of CDHAp/PCL and CDHAp/PLLA beads was determined by the geometrical method. Very low total porosities of 13–15 % were obtained for CDHAp/PCL and CDHAp/PLLA composites. CDHAp+cipro, CDHAp+genta, CDHAp/PLLA samples were prepared using the method described above.

Antibacterial efficiency in Trypticase soy broth (TSB) buffer. The HAp biomaterial disks were firstly eluted in rabbit blood plasma at 37 °C in 5% CO_2 atmosphere and 100% relative humidity for 2 h. Biomaterials of all groups were incubated at 37 °C for 24 h in 2 ml TSB (Oxoid, UK) with 1 ml bacteria suspension. The suspension had optical density of 0.5 according to the McFarland standard. 2 ml TSB bacteria suspension alone with optical density of 0.5 (according to the McFarland standard), was used as the control. After 24 h incubation, to test the antibacterial efficiency of the studied biomaterials, 0.1 ml suspension was cultured on trypticase soy agar (TSA) (Oxoid, UK). In addition, after the incubation, the biomaterials of all studied groups were transferred to new rabbit blood plasma at 37 °C with 5% CO_2 atmosphere and 100% relative humidity for 2 h, and then to a new TSB and bacterial culture suspension for 24 hours. This was every 24 hours for two days. No antibacterial effect was observed in the tested biomaterial groups, as number of TSA colonies was equivalent to that of the control.

Bacterial cultures. Antibacterial efficiency of all biomaterials was tested using *S. epidermidis* (ATCC 12228) and *P. aeruginosa* (ATCC 27853) bacteria reference cultures.

Statistical analysis. The Mann-Whitney test was used to assess statistically significant differences between antibacterial effect of different biomaterial samples. Statistically significant was assumed if p was less than or equal to 0.05. Statistical analyses were performed with software SPSS 22.0.

RESULTS

Antibacterial efficiency tests showed that the mean when time when biomaterial samples with biodegradable polymer and antibiotics had antibacterial effect against *S. epidermidis* and *P. aeruginosa* was significantly longer ($p < 0.01$) than for biomaterial samples with antibiotics against *S. epidermidis* and *P. aeruginosa* and without biodegradable polymer (Fig. 2). No antibacterial properties of HAp/PLLA, CDHAp/PLLA, and CDHAp/PCL samples were observed. Samples with biodegradable PCL show significantly longer ($p < 0.01$) antibacterial effect than samples with biodegradable PLLA for both antibiotics used in the study.

In the first six days of the study (144 h) the growth of *S. epidermidis* was almost completely inhibited in CDHAp/PLLA+cipro and HAp/PLLA+cipro samples. In the following five days, CDHAp/PLLA+cipro and Hap/PLLA+cipro samples released antibiotics, but did not completely inhibit the growth of *S. epidermidis*, and the relative bacterial inhibition gradually decreased. In the first hours of the study, the growth of *S. epidermidis* was completely inhibited in CDHAp+cipro and HAp+cipro samples, however subsequently this effect rapidly decreased (Fig. 3).

The time period of antibacterial effect of HAp/PLLA+genta and CDHAp/PLLA+genta on *S. epidermidis* was longer (Fig. 4) than that of HAp+genta and CDHAp+genta.

Inhibition of *S. epidermidis* growth by CDHAp/PCL+cipro samples was more effective than for CDHAp/PLLA+cipro, as almost complete inhibition continued for an additional two days ($p < 0.01$); almost complete inhibition occurred for eight days (192 hours), with subsequent decrease over five days. The *S. epidermidis* growth inhibition effect of CDHAp/PCL+genta samples was very similar to that of CDHAp/PCL+cipro samples, but its antibacterial efficacy extended for one day longer. CDHAp+genta and CDHAp+

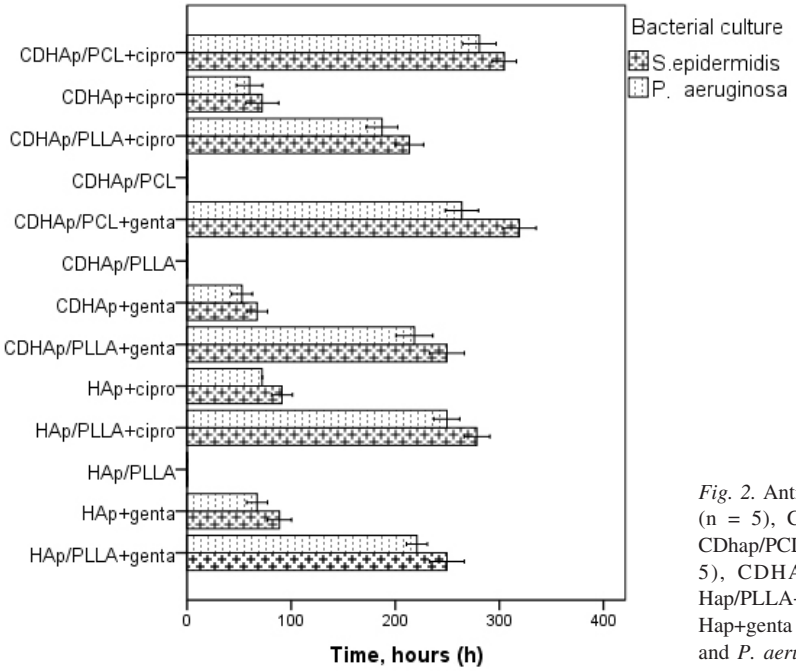

Fig. 2. Antibacterial efficiency *in vitro* testing of CDHAp/PCL+cipro (n = 5), CDHAp+cipro (n = 5), CDHAp/PLLA+cipro (n = 5), CDhap/PCL (n = 5), CDHAp/PCL+genta (n = 5), CDHAp/PLLA (n = 5), CDHAp+genta (n = 5), CDHAp/PLLA+genta (n = 5), Hap/PLLA+cipro (n = 5), Hap+cipro (n = 5), Hap/PLLA (n = 5), Hap+genta (n = 5), Hap/PLLA+genta (n = 5) against *S. epidermidis* and *P. aeruginosa*. Data presented as mean antibacterial time ± SD.

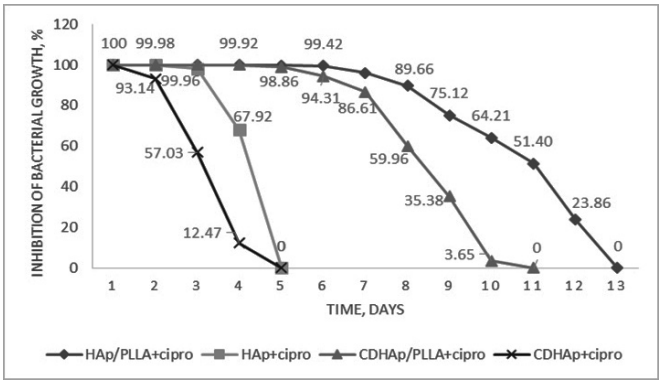

Fig. 3. Dynamics of *S. epidermidis* growth inhibition. Data presented as mean relative (%) bacterial growth inhibition.

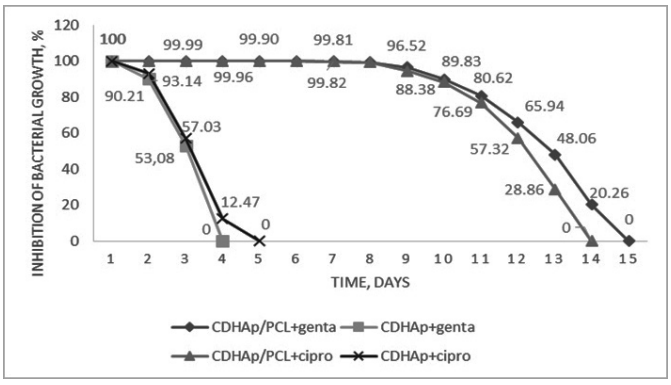

Fig. 5. Dynamics of *S. epidermidis* growth inhibition. Data presented as mean relative (%) bacterial growth inhibition.

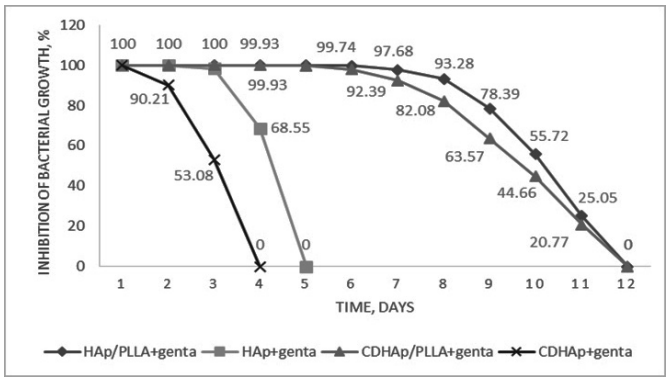

Fig. 4. Dynamics of *S. epidermidis* growth inhibition. Data presented as mean relative (%) bacterial growth inhibition.

cipro samples rapidly lose their ability to inhibit the growth of *S. epidermidis*. (Fig. 5).

Almost complete *P. aeruginosa* growth inhibition by CDHAp/PLLA+cipro samples was observed for four days (96 h). In the subsequent four days, *P. aeruginosa* growth inhibition was gradually reduced, and the time period of antibacterial effect was nine days (187.2 hours). The antibacterial time period of effect of CDHAp+cipro samples was three days; complete *P. aeruginosa* growth inhibition was observed on the first day, and in the next two days there was a rapid decline in the inhibitory effect (Fig. 6). CDHAp/ PCL+cipro samples had a similar effect to that of CDHAp/ PLLA+cipro samples; CDHAp/PCL+cipro samples show significantly longer ($p < 0.01$) antibacterial effect (280.8 hours) and complete inhibition of *P. aeruginosa* growth occurred for and additional three days. (Fig. 7).

There is no significant difference ($p < 0.01$) between antibacterial properties of Hap/PLLA+genta and CDHAp/ PLLA+genta samples against *P. aeruginosa* (Fig. 8).

DISCUSSION

Implant-related infections are among the most common complications associated with any biomaterial infection, re-

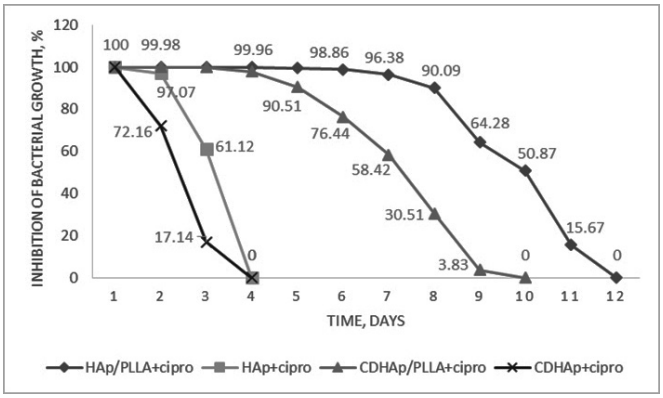

Fig. 6. Dynamics of *P. aeruginosa* growth inhibition. Data presented as mean relative (%) bacterial growth inhibition.

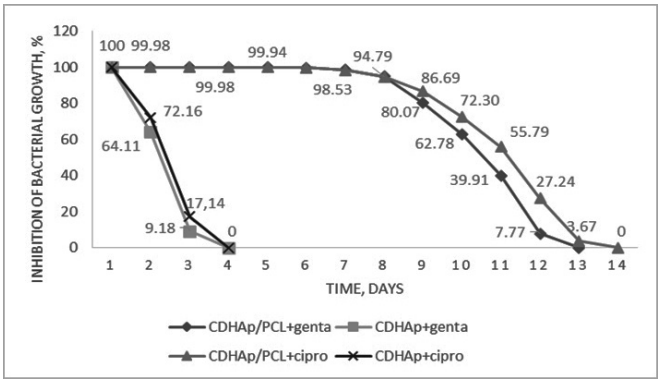

Fig. 7. Dynamics of *P. aeruginosa* growth inhibition. Data presented as mean relative (%) bacterial growth inhibition.

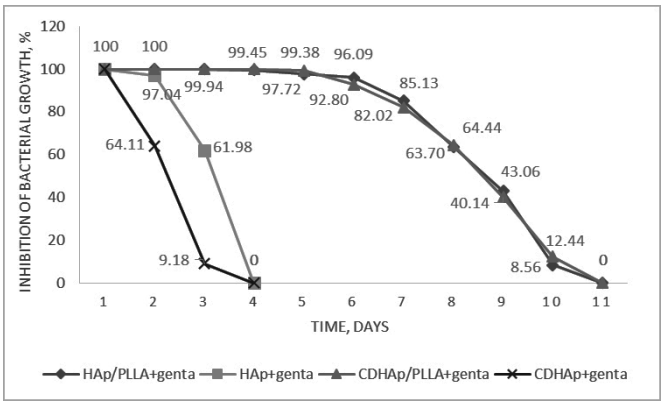

Fig. 8. Dynamics of *P. aeruginosa* growth inhibition. Data presented as mean relative (%) bacterial growth inhibition.

gardless of form or function. These infections usually involve bacterial colonisation and later biofilm formation on biomaterials (Reinis *et al*., 2010). These infections are not susceptible to antimicrobial agents, and are protected by the immune system of the host. In addition, it becomes increasingly clear that the infection in the surrounding tissue plays an important role in implant related infections, and composition and design implanted biomaterials can have an effect on the infection (Busscher *et al*., 2012).

Two main routes are well known when implanted objects become a target of bacteria: 1) direct implant contamination with bacteria during surgical rocedures. Bacteria colonises the surface of biomaterials during surgery. The patient's skin or mucosal microflora, air microflora, or microflora of medical staff could be the source of bacterial contamination; 2) bacteria reaching the implant with haematogenous dissemination, and invoking a late implant infection. The bacterial contamination source is likely skin and mucous membrane microflora (Zimmerli *et al*., 2004).

When bacteria are bound to implanted biomaterials, phenotypic changes occur and bacteria become associated with the surface structure. The attached bacteria begin to secrete an extracellular matrix (glycocalyx) on the implanted biomaterial surface. Glycocalyx encompasses bacterial colonies on the implant, forming a biofilm (Costerton *et al*., 1999).

Antibiotics should be used to prevent biofilm formation on an implanted biomaterial surface. A local antibiotic therapy (biomaterials with antibiotics) should be used in order to avoid systemic complications and other side effects of antibiotics (Li *et* al., 2011; Ruckh *et al*., 2012).

Systemic antibiotic therapy has several disadvantages, such as low bioavailability, poor penetration of antibiotics in bacterial infections in site, side effects, as well as the ability of bacteria to develop resistance to antibiotics (Xu *et al*., 2008; Lepretre *et al*., 2009).

Biomaterials that are impregnated with antibiotics for local antibiotic release can be used to avoid complications from systemic antibiotic usage. A large number of studies have aimed to develop new and effective local antibiotic release systems from biomaterials (Guo *et al*., 2013). In these studies, a wide variety of biomaterials impregnated with different antibiotics have been investigated. Most often these antibiotics are commonly used, incluiding in hospitals to treat and prevent implants from possible infections. Studies on biomaterials that are covered with a biodegradable polymer and antibiotics have demonstrated longer periods of antibacterial effect and protection of the implant from infection. In the present study, we examined two leading causative agents of implant-related infections, which form biofilms (Xiong *et al*., 2012; Jaiswal *et al*., 2015).

The results showed that biomaterial samples covered with biodegradable PLA polymers have longer periods of antibacterial effect and thus they are more effective in protecting an implant from infections, compared to biomaterial samples without a PLLA polymer. A large number of studies have reported similar results, showing that biomaterials with biodegradable polymers maintain antibacterial properties for longer periods of time (Belcarz *et al*., 2009).

Another factor that can affect the period of antibacterial activity is the porosity of biomaterial samples. In our study, samples with higher porosity levels showed more sustained antibacterial properties, and thus needs to be examined in

other studies on implant related infections (Chai *et al*., 2007; Meurice *et al*., 2012).

CONCLUSION

HAp samples with antibiotics and biodegradable polymers ensure slow secretion of antibiotic substances. The polymer (PLLA or PCL) is degraded slowly and it also ensures a slow secretion of antibiotic substances. However, in situations when HAp samples are saturated with antibiotic substances and they are not covered by biodegradable polymers (PLLA or PCL), antibiotics secrete rapidly, thus providing protection from infection for a shorter period of time and increasing risk of developing implant-related infections.

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Received 4 December 2015

BIONOĀRDĀMU POLIMĒRU SATUROŠU UN AR ANTIBIOTISKAJĀM VIELĀM PIESŪCINĀTU BIOMATERIĀLU ANTIBAKTERIĀLĀS EFEKTIVITĀTES NOTEIKŠANA

Infekcijas slimības joprojām ir aktuāla problēma medicīnā, t.sk. jomās, kas saistītas ar biomateriālu implantāciju. Operācijas laikā un arī pēcoperācijas periodā normālās floras baktērijas limfogēnās vai hematogēnās diseminācijas rezultātā var sasniegt implantēto objektu, to kolonizēt un izsaukt infekciju. Biomateriālu bakteriālā kolonizācija sākas ar adhēziju jeb baktēriju piesaisti pie to virsmas, līdz ar to, nomācot šo spēju, var samazināt biomateriālu saistīto infekciju attīstības iespēju. Baktēriju adhēziju pie biomateriāliem var samazināt, izmantojot lokālu antibiotisko vielu izdales sistēmas. Šajā *in vitro* pētījumā tiek izmantoti oriģināli sintezēti biomateriāli ar bionoārdošiem polimēriem un antibiotiskajām vielām, lai samazinātu baktēriju adhēziju un bakteriālo biofilmu veidošanos uz biomateriāliem. Šo biomateriālu antibakteriālā efektivitāte tika pētīta pret biežākajiem pēcoperāciju infekciju ierosinātājiem un biofilmu veidotājiem – *Staphylococcus epidermidis* un *Pseudomonas aeruginosa*. Pētījuma rezultāti parāda, ka biomateriāli ar antibiotiskajām vielām un bionoārdošajiem polimēriem uzrāda ilgākas antibakteriālās īpašības nekā biomateriāli ar antibiotiskajām vielām bez bionoārdošā polimēra pret abām baktēriju kultūrām. Tādējādi biomateriāli ar antibiotiskajām vielām un bionoārdošu polimēru ir pasargāti no baktēriju adhēzijas un sekojošu biofilmu veidošanās ilgākā laika periodā.