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IN VIVO ASSESSMENT OF THE BIOCOMPATIBLE PROPERTIES OF RESORBABLE POROUS MATERIALS FOR PLEURAL IMPLANTATION

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Correcting the pleural cavity space or filling large residual cavities (up to 500–700 cm^3), arising as a result of extensive combined resections of the lung or extrapleural pneumolysis in tuberculosis and other lung diseases, still remains a challenging issue. The surgical methods used to correct the pleural cavity space are traumatic in nature. Moreover, various biological and synthetic materials used are not effective enough. **Objective:** to conduct an in vivo study of the biocompatible properties of laboratory samples of porous materials based on polylactide (PLA) and polycaprolactone (PCL) as potential materials for pleural implants development, as part of the general problem of developing a resorbable porous implant for intra- and extrapleural implantation and in situ formation of a "biological filling" to correct the volume of the pleural cavity. **Materials and methods.** In vivo subcutaneous implantation was performed in Wistar rats. The experiment involved the following samples: No. 1 – 3.0%; No. 2 – 4.0%; No. 3 – 1.7%. The ratio of the polymers in the solution was, respectively: 3/1, 1/3 and 1/1 PLA/PCL. Highly porous implants were obtained by lyophilization. The porosity of the samples ranged from 96.0% to 98.3%. The Young's modulus was from 100 to 1800 kPa. In the control group, a Mentor silicone implant shell was used. The explantation time was 1, 2, 3, 4, 5, 8, 12, 14 weeks. Histological, histochemical and immunohistochemical studies of explants and surrounding local tissues were conducted. **Results.** Reaction of local tissues to the implantation of three types of samples of different composition from PLA/PCL, accompanied by material resorption processes, replacement by fibrous tissue, vascularization and encapsulation, without perifocal inflammation and reactive changes, indicates the biocompatibility of the materials studied. In control samples with silicone implant, a long-lasting perifocal reaction from eosinophilic leukocytes was revealed, which prevents us from excluding the possibility of an allergic reaction to the implant material in the surrounding tissues. **Conclusion.** In vivo experiments on the small animals show the biosafety and high biocompatibility of laboratory samples of bioresorbable highly porous matrices based on polylactide and polycaprolatcon as potential materials for development of pleural implants. Further studies with scaling of laboratory samples and a detailed study of the dynamics of biodegradation of porous matrices in vivo in large animals are required. The need for further improvement in laboratory samples of bioresorbable pleural implants is associated with giving the porous matrices antibacterial, bioactive and X-ray contrast properties.

Keywords: polylactide (PLA), polycaprolactone (PCL), bioresorbable materials, pleural implant, biocompatibility, extrapleural implantation, interpleural implantation, local tissue response to implants.

INTRODUCTION

In thoracic surgery, particularly in pulmonary tuberculosis surgery, there has long been the problem of correcting the pleural cavity volume, or filling large residual cavities (up to 500–700 cm^3) resulting from surgical intervention – extensive combined lung resections or extrapleural pneumolysis. The surgical methods used to correct the pleural cavity volume, such as one-stage or delayed thoracoplasty, used so far, are traumatic, accompanied by chest deformity and severe postoperative pain syndrome [1–4].

Over the entire period of existence of extrapleural pneumolysis surgery and correction of the pleural cavity volume after combined lung resections, about a hundred different methods have been proposed using various

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biological and synthetic materials. However, all of them have proved to be insufficiently effective [5–10].

Implantable biological materials, such as collagen, collagen sponges, structured collagen, fibrinogen, gelatin, hyaluronic acid, etc., have fast resorption timeframe that is insufficient for manifestation of a collapsosurgical effect.

Among synthetic materials, polyurethane foam, fiberglass, polymethylmethacrylate, polystyrene, silicone, etc. have been used. In recent years, silicone prostheses and expanders, designed for reconstructive and plastic breast surgery, have proven to be the best [11–14].

In the last decade, there has been a trend towards wider clinical use of resorbable implants in various surgical specialties. For instance, in maxillofacial surgery, neurosurgery, traumatology, orthopedics, and dentistry, resorbable implants based on polymers and copolymers of glycolic and lactic acids are replacing titanium metal implants. More complex polymer compositions combining different synthetic and biological polymers, as well as various bioactive preparations are also used.

One of the advantages of resorbable implants is that once the healing effect is achieved, the implant does not require additional surgery to remove it. After a certain time, the implant undergoes bioresorption; polymer degradation products are harmless to the body. It should be noted that currently in Russia there are no registered implants for targeted use in thoracic surgery, particularly in pulmonary tuberculosis surgery.

The main requirements for the properties of a pleural implant are: low specific gravity, compliance of the Young's modulus of the implant with the elasticity modulus of the soft tissues of the chest, hydrophobicity of the main volume in combination with hydrophilicity of the surface layer, controllability of implant resorption time, ability to be replaced in the process of resorption by its own tissue, ability to neovascularization.

Synthetic polymers, polylactide and polycaprolactone, are part of various resorbable materials and implants used in maxillofacial surgery, traumatology and orthopedics, as well as in endovascular surgery. Despite the active use of fibers and molded products based on these polymers in medicine, there are few studies on porous materials [15–17]. Also, unlike the known porous materials based on proteins and polysaccharides, medical products made of polylactide and polycaprolactone are resorbed at a significantly lower rate, which is important for their long-term functioning as a pleural filling.

Objective: to conduct an in vivo study of the biocompatible properties of laboratory samples of bioresorbable highly porous matrices based on polylactide (PLA) and polycaprolactone (PCL) as potential materials for the development of pleural implants.

CHARACTERISTICS OF THE STUDY OBJECTS

The following were chosen as starting materials: poly(L-)lactide (PLA) 4032D "*Nature Works*" with 200 kDa average molecular weight (Mw) and ~2 polydispersity index (PDI); polycaprolactone (PCL) No. 440744 "*Sigma Aldrich*" with 80 kDa number average molecular weight (Mn) and ~2 polydispersity index (PDI).

At the department of nanobiomaterials and structures, Kurchatov Institute, laboratory samples of porous materials of three compositions were prepared at on the basis of the developed technology by freeze-drying of frozen solutions of a PLA/PCL polymer mixture in 1,4-dioxane: sample No. 1, containing 3 wt.% of PLA/PCL mixture in initial solution with a 3/1 polymer ratio; sample No. 2, containing 4 wt.% PLA/PCL with a 1/3 ratio and sample No. 3, containing 1.7 wt.% of a mixture of PLA/PCL polymers in an initial solution with a 1/1 ratio (Fig. 1, a, b).

Regardless of the composition, all three samples have a branched structure with interpenetrating pores. A typical photomicrograph of a cut of the material is shown in Fig. 1, c. The average pore sizes are 100–150 μm.

The mechanical properties of spongy materials significantly depend on both the porosity of the materials and the polymer composition. Due to the fact that the glass

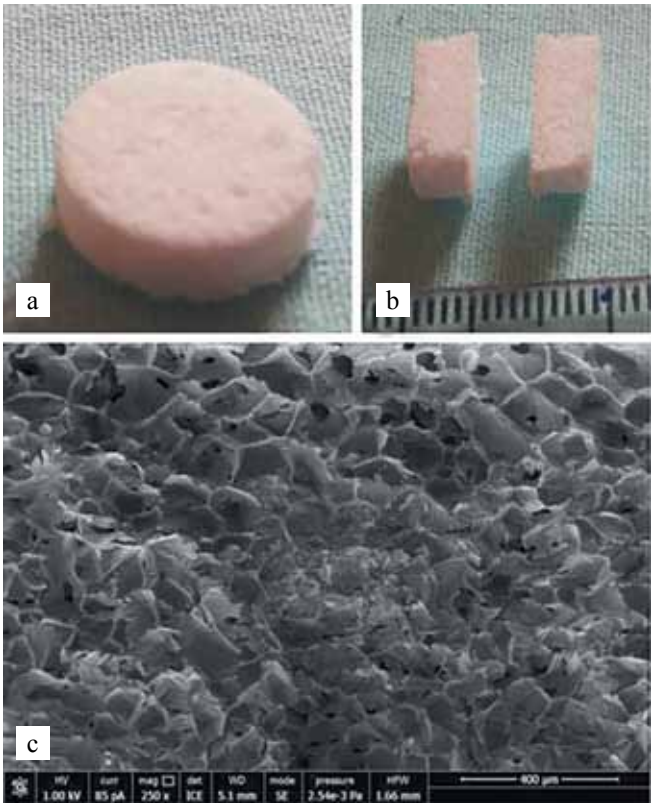

Fig. 1. Appearance and electron microscopy of the PLA/PCL sample: a) appearance of the laboratory sample 1.7% PLA/PCL 1/1; b) cross-section of the laboratory sample 1.7% PLA/PCL 1/1; c) scanning electron microscopy of a slice of a spongy material based on polylactide obtained by cryolyophilization. Accelerating voltage 1 kV

transition temperature of polycaprolactone lies around –60 °C, adding it decreases the elastic modulus of the material. Thus, the mechanical properties can be tuned over a wide range of values. For the spongy materials discussed in this paper, the elastic moduli are 1800 ± 250 kPa (Sample 1), 1240 ± 320 kPa (Sample 2), and 97.7 ± 9.5 kPa (Sample 3). The samples were sterilized by radiation with 1.5 Mrad maximum dose.

At the next stage, in vitro studies of hemolytic, cytotoxic, and matrix properties as well as a study of biodegradation of laboratory samples in a model environment were carried out at the department of biomedical technologies and tissue engineering, Shumakov National Medical Research Center of Transplantology and Artificial Organs.

Hemolytic properties were examined on an extract obtained from experimental samples of sponges using rabbit red blood cell mass. Data (percentage of hemolysis is less than 2) obtained from the study suggests that the extract of experimental samples of sponges from PLA and PCL is free of hemolytically active substances, while the product itself has no hemolytic effect and meets the requirements for medical devices according to GOST ISO 10993-4-2011 "Research on devices that interact with blood".

Cytotoxicity studies were performed on a test-culture of NIH/3T3 mouse fibroblast cells. Matrix properties were examined on a culture of human adipose tissue-derived mesenchymal stem cells. Results from these studies suggest that the experimental samples of PLA and PCL sponges have no cytotoxic effect. However, the surface of the sponges studied does not have sufficient matrix properties, poorly supports cell adhesion, and does not provide the necessary cell proliferation conditions. Hydrophilization of the sponge surface may be a promising approach for improving the matrix properties of a material. In order to verify this assumption, some samples were selected for hydrophilization of their surface with gelatin. With the subsequent re-experiment on the cultivation of human adipose tissue-derived mesenchymal stem cells. In this case, the matrix properties of the sponges improved significantly.

In the biodegradation study, samples of porous matrix were incubated statically at 37 °C in 20 mL of 0.025 M phosphate-buffered saline containing nipagin and nipazole at 0.06% and 0.02% concentrations, respectively. Weight loss due to degradation was recorded gravimetrically on an analytical balance. The buffered saline solution was replaced with a fresh one every 2 weeks. The PLA/PCL porous samples were found to be resistant to biodegradation in phosphate-buffered saline at 37 °C for 26 weeks. This suggests that the volume and shape of laboratory samples can be maintained in planned long-term in vivo studies.

IN VIVO BIOCOMPATIBILITY ASSESSMENT METHODS

In the study of biocompatibility in vivo, we used subcutaneous implantation of samples into Wistar rats (total number of animals n = 8). All studies on laboratory animals were carried out in strict accordance with the laws of the Russian Federation (the Rules of Laboratory Practice, approved under Order No. 708 of the Ministry of Health of Russia, dated August 23, 2010, as well as the GOST R ISO 10993-2-2009 standard "Medical Devices. Assessment of the Biological Action of Medical Devices. Part 2. Requirements for Animal Welfare") and in compliance with the biotic principles approved by the European Convention for the Protection of Vertebrate Animals, 2005.

The implanted samples were disc-shaped porous materials with 5 mm diameter and 3 mm thickness.

The experimental research methodology was as follows. After 1.0 mL of ketamine was injected intramuscularly on the previously epilated and treated skin of the back, an incision was made along the midline with a length of about 4 cm. Then soft tissues were bluntly dissected in the corners of the wound and in different directions, soft tissues were stratified up to the muscle fascia, forming four implant beds, one placed in each bed, and a fragment of the silicone implant capsule was placed in the fourth bed. The distance between the implanted samples was about 4 cm. After the implant has been placed, each bed was isolated by suturing with an atraumatic non-absorbable 4/0 prolene thread.

The animals were taken out of the experiment by an overdose of ether anesthesia. The explanation periods were: 1, 2, 3, 4, 5, 8, 12, 14 weeks (one animal per explantation point). At autopsy, the macroscopic picture of the implantation area and the condition of the implants themselves were assessed, after which the tissues of the implanted area were taken for further morphological examination.

MORPHOLOGICAL EXAMINATION

Tissue materials were fixed in 10% neutral formalin, performed based on a standard technique. Histological sections, 3–5 microns thick, were prepared. The following histological stains were used: hematoxylin and eosin for observational microscopy of implants with adjacent soft tissues and skin; histochemistry – elastica Van Gieson's stain to detect fibrotic processes, fibrous structures; Brachet stain to detect plasma cells in the infiltrate. In addition, an immunohistochemistry with the *CD34* antibody was performed to assess implant vascularization.

RESULTS AND DISCUSSION

Macroscopic assessment of implants and local tissues showed that during the first two weeks, external examination of animal skin in the area of implantation of resorbable porous materials (samples No. 1, 2 and 3 – PLA/PCL) showed no visual signs of the presence of implants in the subcutaneous fascia. On palpation, the implants were well defined, their consistency was assessed as soft-elastic. The skin over the implants was mobile, with no signs of inflammation.

At week 6–14, there was a gradual thickening of the soft tissues of the implantation area with transformation from soft-elastic to dense-elastic consistency. At the same time, in the studied areas, mobility of the skin and soft tissues in the studied areas was preserved, and the implant contours were more clearly defined.

In the silicone implant area, the changes are not very pronounced, apparently due to its thickness (1 mm); there are practically no changes in the dynamics of palpation at different study periods; soft tissue mobility is preserved.

During explantation at all implantation periods, examination of the surrounding tissues (muscles, subcutaneous fascia, skin) showed no macroscopic signs of inflammation. The surface of muscles and fascia was smooth, shiny, elastic consistency, that is, there were no signs of inflammation. The dynamics of macroscopic changes in the implant itself consists in gradual impregnation from the periphery to the center with tissue fluid and a change in the structure of the implant substance: if the porous structure of the implant was well differentiated in the early stages, then by the end of the observation, the implants were completely replaced by grayish fibrous tissue; capillaries were visually traced both on the surface and in the implant thickness (Fig. 2, a, b). The silicone implant did not change outwardly in dynamics, it retained its structure – colorless, transparent, with a smooth shiny surface (Fig. 2, c).

Thus, macroscopic examination revealed that during the experiment, the inflammatory response of the surrounding tissues to implantation of samples (samples No. 1, 2 and 3 – PLA/PCL) was practically identical, weakly expressed and practically disappears within a month; the implant material underwent changes, and silicone implants were almost identical at different explantation periods.

Microscopic examination of samples of bioresorbable highly porous matrix (samples No. 1, 2 and 3 – PLA/PCL) showed that a week after implantation, there was a slight edema of the adjacent muscles and fascia around them, mild or moderate diffuse focal infiltration, and the density of the infiltrate near the implant was higher. The cellular composition of the inflammatory infiltrate was polymorphic. It was dominated by macrophages, in some places with an admixture of lymphocytes, single plasma cells, and eosinophilic leukocytes (Fig. 3). Eosinophilic leukocytes were sporadic and were found only in separate fields of view (1–5 cells at 400× magnification). Within a month, the nature of the infiltrate changed to mononuclear and was represented by macrophages, lymphocytes, and plasma cells. Severity of inflammatory infiltration was regarded as minimal.

The dynamics of changes in the material of the implanted samples in response to the reaction of the surrounding tissues to foreign material did not depend on their composition. A week later, there was mild granulomatous reaction around all the samples; multinucleated

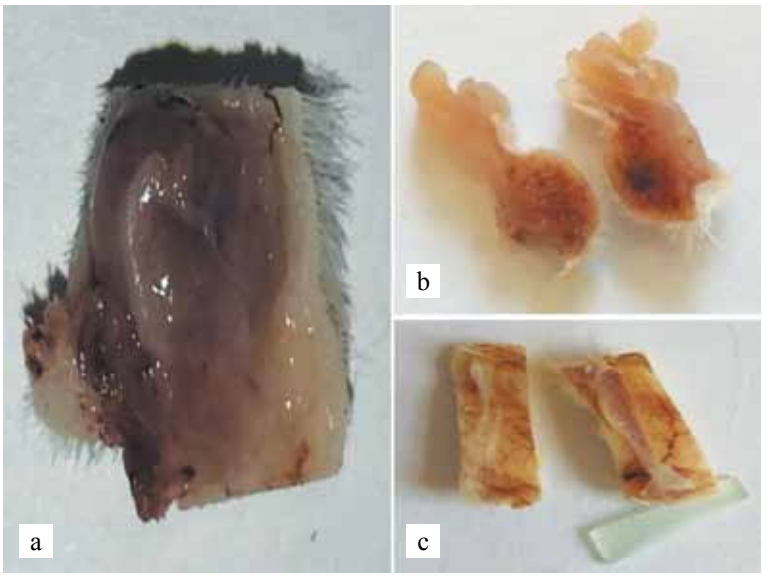

Fig. 2. Macro-preparations of PLA/PCL subcutaneous implants: a) subcutaneous implant 3.0% 3/1 PLA/PCL, 9 weeks, with capillaries on the surface; b) subcutaneous implant 3.0% 3/1 PLA/PCL, 14 weeks, replacement of the implant material by grayish fibrous tissue; c) silicone implant, 14 weeks, unchanged implant structure

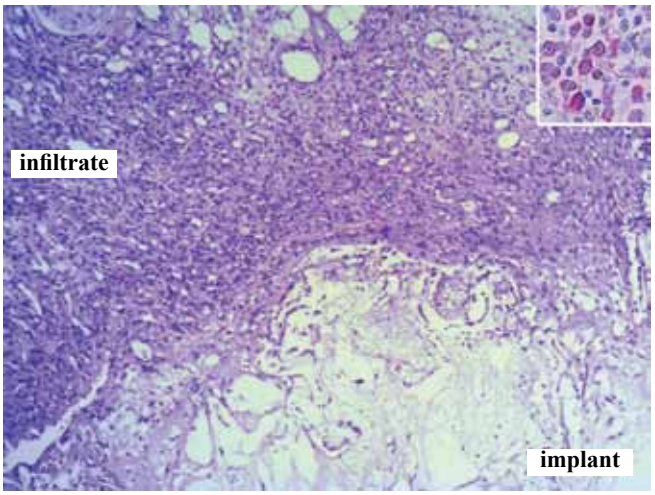

Fig. 3. Perifocal exudative reaction in the soft tissues surrounding the PLA/PCL implant (inset – plasma cells in the infiltrate). H&E stain. 100× magnification; inset – Brasch staining. 400× magnification

foreign body giant cells (FBGCs) with signs of phagocytosis of the implant material were present (Fig. 4, a, b). No capsule formation around the implants was detected. There were also no signs of implant vascularization at this period.

Two weeks after implantation, in the samples of bioresorbable highly porous matrix (samples No. 1, 2, and 3 – PLA/PCL), single small capillaries were detected in areas of the forming granulation tissue, which were located between foreign body granulomas along the implant periphery. Immunohistochemistry with the CD34 antibody showed positive expression in the basement membrane of small vessels located in the implant thickness (Fig. 5), which confirmed the presence of vascularization signs.

Four weeks after implantation, there was a subtotal granulomatous reaction with a large number of FBGCs, with partial replacement of implants with fibrous tissue,

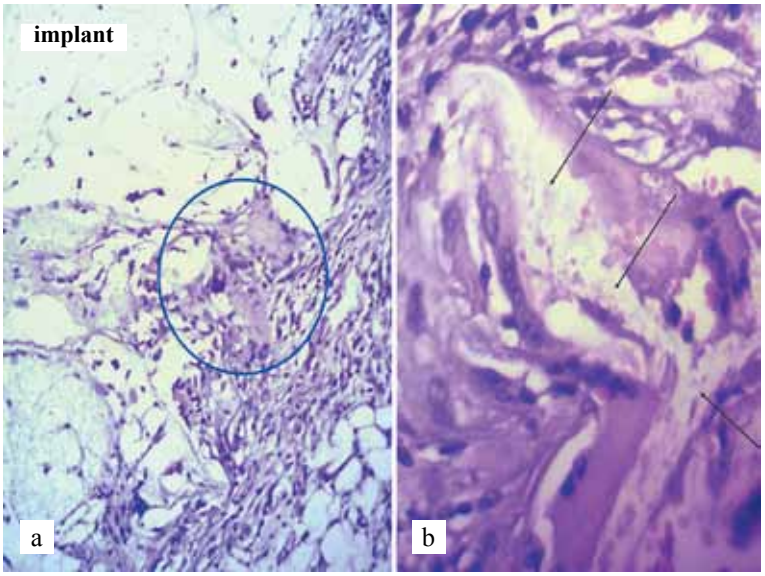

Fig. 4. Morphological picture 1 week after PLA/PCL implantation: a) forming foreign body granuloma inflammation on the periphery of the PLA/PCL implant (circled). H&E stain. 200× magnification; b) giant foreign body cell with signs of phagocytosis of the PLA/PCL implant material (phagocytosed material is indicated by arrows). H&E stain. 1000× magnification

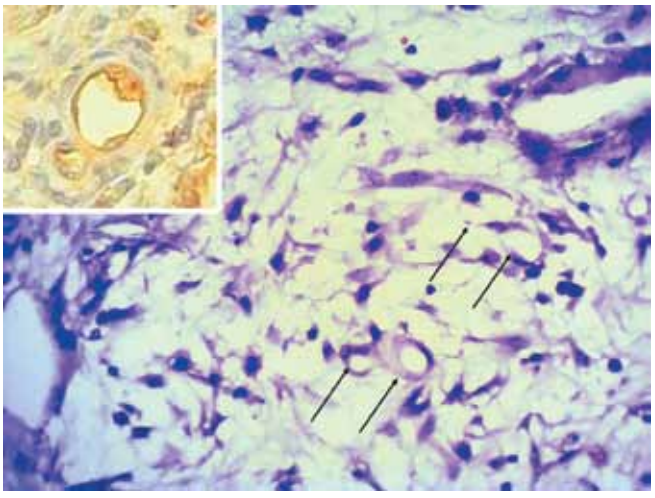

Fig. 5. Morphological picture 2 weeks after PLA/PCL implantation. Initial signs of vascularization of PLA/PCL implant material, formation of single capillaries (capillaries are indicated by arrows). H&E stain. 400× magnification; inset – capillary in the implant (immunohistochemical study with CD34 antibody)

which was confirmed by histochemical examination with Van Gieson stain. There were vascularization phenomena (beginning of vascularization from week 2) and formation of a thin, in some places loose connective tissue capsule around the implant (Fig. 6, a, b, c, d).

After 8 weeks, the implants were almost completely replaced by fibrous tissue; the Van Gieson stain revealed both the presence of diffusely located collagen fibers with small, preserved areas of granulomatous inflammation (such as foreign bodies) between them, and micro areas of focal fibrosis. Microparticles of phagocytosed implant material were found in the FBGC cytoplasm. There was vascularization of the whole implant volume with detection of sinusoidal capillaries and thin-walled vessels, with the presence of erythrocytes in their lumen. There was a thin fibrous capsule formed around the implants, well defined by both observational microscopy and van Gieson stain.

After 12 weeks, the implants were completely replaced with fibrous tissue with a clear formation of multidirectional bundles of collagen fibers with a small amount of FBGCs interfascicularly, with signs of phagocytosis of the sample material located between the collagen fibers. Signs of vascularization were well expressed in the form of full-blooded sinusoidal capillaries and vessels. There was no perifocal inflammatory response in the soft tissues.

After 14 weeks, there was a complete replacement of the bioresorbable highly porous matrix implants (samples No. 1, 2 and 3 – PLA/PCL) with fibrous tissue, with almost complete absence of granulomatous inflammation. Single foreign body giant cells remained between collagen fibers. The implants were completely vascularized throughout the entire thickness. A fibrous capsule was formed in all samples. No inflammation or calcification was observed in the samples and adjacent soft tissues (Fig. 7, a, b, c; Fig. 8).

With silicone implantation (a fragment of the silicone breast implant shell), the fibrous capsule was well defined *after two weeks*. Note that a small diffuse cellular infiltration with predominance of eosinophilic leukocytes (up to 50 eosinophilic leukocytes per field of view at 400× magnification) was detected in the adjacent fascia of the silicone implant, with an eosinophilic reaction of approximately the same severity in the infiltrate at early stages of implantation (one week).

After 8 weeks (2 months), the structure of the implant material was completely preserved; there was no replacement with fibrous tissue, there was practically no granulomatous reaction (only isolated very small fuzzy

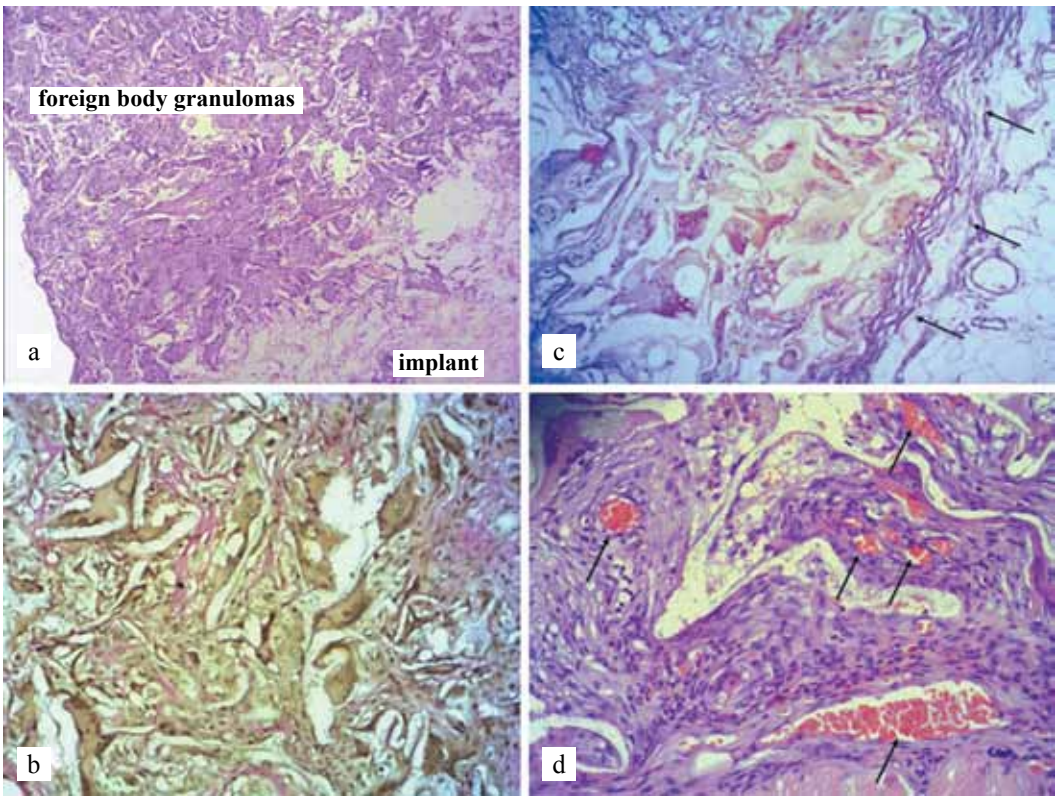

Fig. 6. Morphological picture 4 weeks after PLA/PCL implantation: a) subtotal replacement of the PLA/PCL implant by foreign body granulomas. H&E stain. 200× magnification; b) partial replacement of the PLA/PCL implant by connective tissue; red-stained fibrous fibers located between the foreign body granulomas. Van Gieson's stain. 400× magnification; c) forming capsule around the PLA/PCL implant (indicated by arrows). Van Gieson's stain. 400× magnification; d) vascularization of the PLA/PCL implant, sinusoidal capillaries and vessels (indicated by arrows). H&E stain. 400× magnification

macrophage granulomas were detected); no signs of vascularization were found.

After 14 weeks (3.5 months), the capsule was formed, the implant was still completely intact. There was no foreign body granulomatous reaction, no signs of vascularization, or replacement of the implant with fibrous tissue. There were no reactive inflammatory and exudative phenomena in the adjacent soft tissues (muscles, fatty tissue, fascia, skin with subcutaneous fatty tissue) (Fig. 9, a, b, c).

Thus, reaction of local tissues to the implantation of three types of samples of different composition from

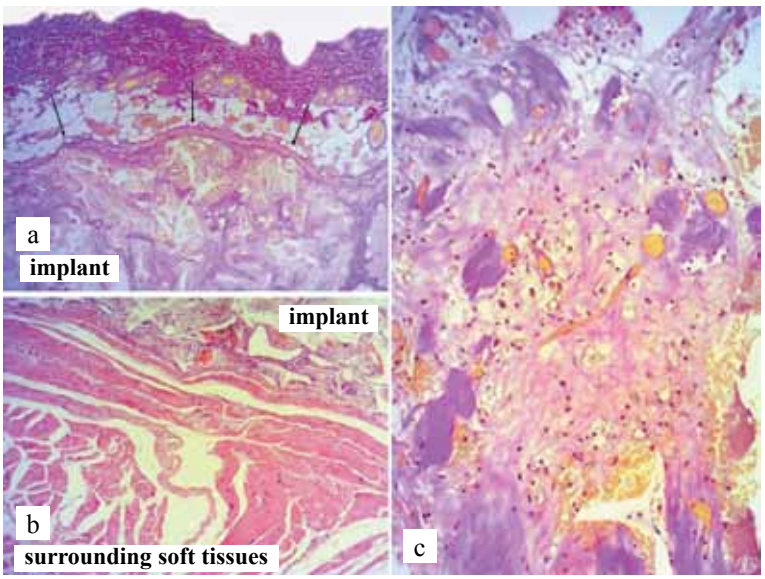

Fig. 7. Morphological picture 14 weeks after PLA/PCL implantation: a) capsule formed around the PLA/PCL implant (indicated by arrows). Van Gieson's stain. 100× magnification; b) absence of inflammatory infiltrate in the soft tissues surrounding the PLA/PCL implant. H&E stain. 100× magnification; c) replacement of PLA/PCL implants by fibrous tissue with almost complete absence of foreign body granuloma inflammation. Van Gieson's stain. 200× magnification

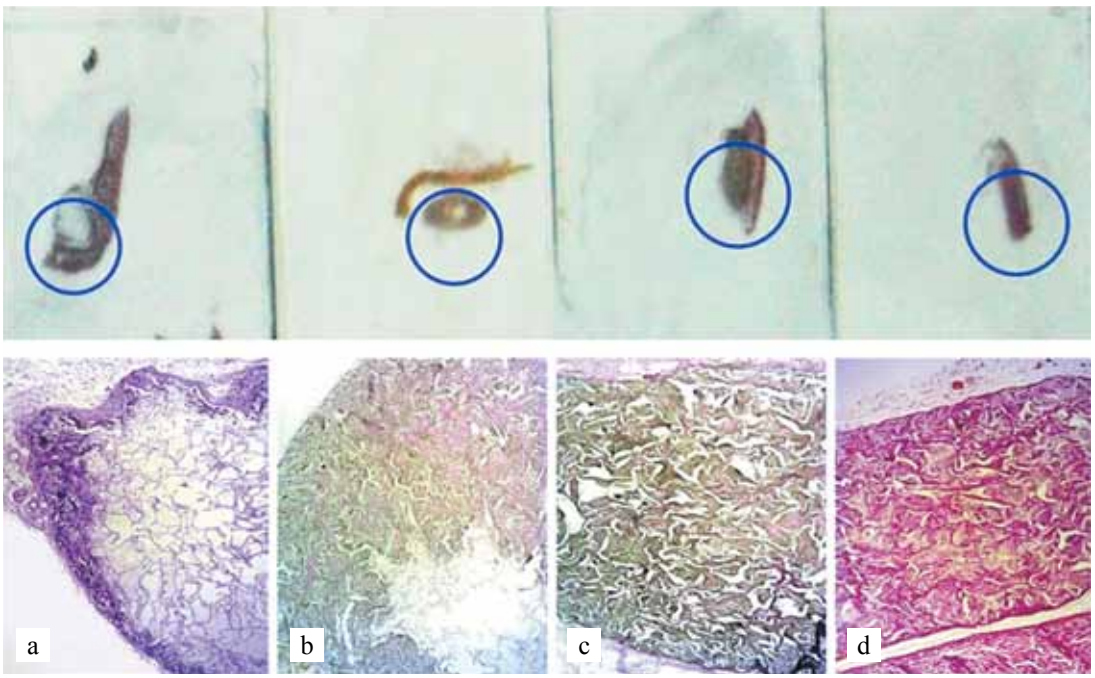

Fig. 8. Dynamics of morphological changes in PLA/PCL implants in the period from 1 to 14 weeks. Upper row – macro preparations, implant with surrounding soft tissues. Bottom row – microscopic preparations (1 week – H&E stain; other preparations – Van Gieson's stain. 100× magnification): a) 1 week – marginal granulomatous reaction of foreign bodies in the implant; b) 4 weeks – subtotal replacement of the implant by foreign body granulomas; c) 8–12 weeks – complete replacement of the implant by foreign body granulomas with fibrous tissue formation; 14 weeks – replacement of the implant by fibrous tissue with single foreign body granulomas

PLA/PCL, accompanied by processes of material resorption, its replacement by fibrous tissue, vascularization, and encapsulation, without perifocal inflammatory process and reactive changes, indicates that the studied materials are biocompatible.

When using a silicone implant, the structure of its material remains unchanged, granulomatous resorption reaction is practically not formed and is detected along the periphery of the sample for several weeks. Fibrosis of the implant was not detected, but there was a delimitation of its well-formed fibrous capsule, which began to form a week earlier than in the rest of the experimental samples. There was pronounced reaction of eosinophilic leucocytes in the adjoining soft tissues for a long time, which may indicate an allergic effect of the implant material on the macroorganism tissues.

FINDINGS:

1. A comprehensive morphological study of bioresorbable highly porous matrix samples (samples No. 1, 2 and 3 – PLA/PCL) using histochemical and immunohistochemical techniques showed no differences in cellular and tissue reactions of porous matrices with different PLA/PCL ratios.
2. During the first month (from 2–3 weeks of implantation), there started the formation of a capsule around the implant (PLA/PCL), development of a foreign body granulomatous reaction in the peripheral parts of the implant, spreading into the thickness of the implanted material, with signs of pronounced phagocytosis, which indicated cellular biodegradation of the implant material.
3. Starting from week 2 after implantation, implant vascularization was noted, which was confirmed via immunohistochemistry. The study of implants over time showed their gradual replacement with fibrous tissue at week 12–14 and a good neovascularization.
4. Reaction of surrounding tissues was identical in all samples (PLA/PCL), was poorly expressed, manifested by focal edema and small focal cellular lymphoid or lymphoid-eosinophilic infiltration. Perifocal reactive changes disappeared within a month after implantation.
5. In control samples with a silicone implant, there was no bioresorption of the material and no neovascularization process was detected. There was a long-lasting rather pronounced perifocal reaction from eosinophilic leukocytes, which does not exclude the possibility of an allergic effect of the implant material on adjacent tissues.

CONCLUSION

The in vivo experimental work conducted on small animals showed the biosafety and high biocompatibility of laboratory samples of a bioresorbable highly porous matrix as potential materials for pleural implants. Further studies with the scaling of laboratory samples, as well as a detailed study of the dynamics of biodegradation of porous matrices in vivo in large animals are required. Further improvement in laboratory samples of bioresorbable highly porous implants is associated with imparting

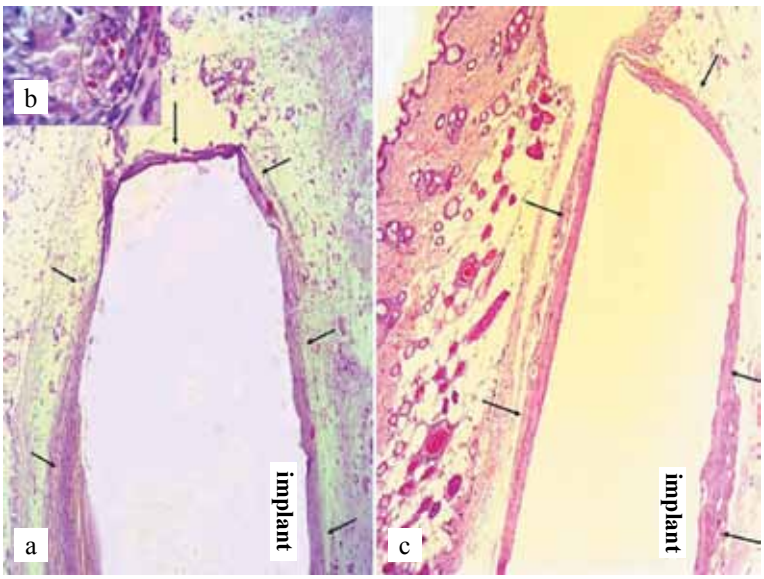

Fig. 9. Morphological picture 4 and 8 weeks after implantation of a fragment of the silicone capsule of Mentor breast implant: a) silicone implant, 4 weeks, intact, with a thin fibrous capsule (indicated by arrows). H&E stain. 100× magnification; b) in the soft tissues surrounding the silicone implant, eosinophilic reaction (eosinophilic leukocytes are surrounded by a round frame). H&E stain. 1000× magnification; c) silicone implant, 8 weeks, intact, with formed fibrous capsule (indicated by arrows). H&E stain. 100× magnification

antibacterial, bioactive and X-ray contrast properties to porous matrices.

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The authors declare no conflict of interest.

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