9. Goldina I.A. Gaidul K.V., Kozlov V.A. Epigenetic mechanisms of multiple sclerosis. Open Access Journal of Translational Medicine and Research. 2018;2(2):56-61.

10. Goldina I.A., Safronova I.V., Goldin B.G., Gaidul K.V. Pattern of relationship of the level of mRNA of human endogenous retrovirus of class I *λ4-1envelope* gene and proliferative activity of blood mononuclear cells.International Immunology. 2010;22(S1):P. i71.

11. Grandi N., Tramontano E.HERV envelope proteins: physiological role and pathogenic potential in cancer and autoimmunity. Front. Microbiol.2018; 9:462. Doi:10.3389/fmicb.2018.00462.

12. Hurst T.P., Magiorkinis G. Epigenetic control of human endogenous retrovirus expression: focus on regulation of long-terminal repeats (LTRs). Viruses.2017;9:1–13. Doi:10.3390/v9060130.

13. Ramasamy R., Joseph B., Whittall T.Potential molecular mimicry between the human endogenous retrovirus W family envelope proteins and myelin proteins in multiple sclerosis. Immunol. Lett. 2017;183:79–85. Doi:10.1016/j.imlet.2017.02.003.

14. McDonald J.J., Weller B., O'Neil M. Scottish MS Register Study Collaborators. Latitudinal variation in MS incidence in Scotland.Mult. Scler. Relat. Disord. 2019;32:116-22. Doi:10.1016/j.msard.2019.04.032.

15. Ito J., Sugimoto R., Nakaoka H., Yamada S., Kimura T., Hayano T., Inoue I. Systematic identification and characterization of regulatory elements derived from human endogenous retroviruses. PLoS Genet. 2017;13(7):. e1006883. Doi:10.1371/journal.pgen.1006883.

16. Marrie R.A., Reingold S., Cohen J., Stuve O, Trojano M, Sorensen PS, Cutter G, Reider N. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. 2015;21(3):305-17. Doi:10.1177/1352458514564487.

17. Volkman H.E.,Stetson D.B. The enemy within: endogenous retroelements and autoimmune disease. Nat. Immunol.2014;15(5):415-22. Doi:10.1038/ni.2872.

18. Yi J.M.,Kim H.S. Molecular phylogenetic analysis of the human endogenous retrovirus E *(HERV – E)* family in human tissues and human cancers. Genes Genet. 2007; 82(1):89-98.

L.V. Antonova, A.V. Mironov, V.N. Silnikov, T.V. Glushkova, E.O. E.O. Krivkina, T.N. Akentyeva, M.Yu. Khanova, V.V. Sevostyanova, Yu.A. Kudryavtseva, L.S. Barbarash

BIODEGRADABLE VASCULAR PATCHES: A COMPARATIVE DESCRIPTION OF PHYSICOMECHANICAL AND HEMOCOMPATIBLE PROPERTIES

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УДК 616-77:577.11:57.085.23

RGD-modification is a promising approach to improve biocompatibility of biodegradable vascular patches, potentially suitable for arteriotomy. Vascular patches are electrospun from the blend of polycaprolactone and polyhydroxybutyrate/valerate and modified with RGDK, AhRGD and c[RGDFK] peptides using 1.6-hexamethylene diamine or 4.7.10-trioxa-1.13-tridecanediamine linkers. Their mechanical properties and hemocompatibility are assessed. As the benchmark samples we used human internal mammary artery and xenopericardial KemPeriplas-Neo patches that are routinely used for carotid endarterectomy. Tensile properties of both polymer and biological samples differ from that of native human internal mammary artery. Tensile strength and Fmax of KemPeriplas-Neo patches are 4- and 16.7-times higher ($p < 0.05$). Both, RGD-modified and unmodified PHBV/PCL, demonstrate results similar to human internal mammary artery. Young's modulus of KemPeriplas-Neo patches corresponds to that of native vessels, whereas in polymer patches it exceeds 9 times that of the last ($p < 0.05$). RGD-modified PHBV/PCL patches and original PHBV/PCL patches demonstrate few lysed red blood cells and mild platelet aggregation than KemPeriplas-Neo patches, indicating a high biocompatibility of polymers and modifying agents used to make vascular patches.

Keywords: tissue engineering, biodegradable polymers, vascular patches, surface modification, RGD-peptides.

Introduction. High prevalence of internal carotid artery atherosclerosis and advanced diagnosis have resulted in an increase in the number of carotid endarterectomy performed annually [10]. Carotid stenosis is commonly treated with medical therapy, carotid endarterectomy (CEA), and stenting [13]. Despite recent advances and emergence of minimally invasive techniques, CEA remains the preferred method for treating patients with carotid stenosis.

Randomized controlled trials on the effectiveness of PTFE, Dacron and bovine pericardial patches have shown a similar rate of complications in the long-term period [3]. Thus, patches used in the routine clinical practice does not fully correspond to all needs of vascular surgery, that necessitates the development of new materials and approaches to the design of advanced vascular patches.

The emergence of regenerative medicine has opened new horizons for tissue engineering approaches in the development of bioresorbable materials activating the regenerative potential of the body to restore the damaged vessel walls [15]. Synthetic biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolatone (PCL) are widely used for this purpose [2, 11].

Synthetic polymers may be combined with the natural ones to increase the biocompatibility of the resultant product. Several studies reported the development of tissue-engineered vascular patch made from PGA and coated with poly-4-hydroxybutyrate (poly-4-hydroxybutyrate, P-4-HB). Tissue-engineered pulmonary artery augmentation patches derived from autologous circulating EPC and bone marrow–derived MSC functioned in vivo for up to 6 weeks in the ovine model grossly resembled the structure of the native pulmonary artery [12].

Although cell seeding on a matrix increases its in situ remodeling rate, this approach is generally considered as time-consuming and expensive. Therefore, it seems relevant to develop a self-assembling biodegradable material able to independently populate cells in situ. Moreover, the rapid formation of endothelial monolayers on the inner surface of the patches requires options for its stimulation. Both physical and chemical modifications of the tissue-engineered matrix surfaces are known. They produce proangiogenic effects and contribute to the endothelial cell seeding from the blood flow and surrounding tissues [1, 5, 8]. Thus, new functional biocompatible patches ensuring the regeneration of the damaged vessel wall are of paramount importance.

The **aim** of our study was to develop biodegradable vascular patches modified by various RGD peptides, and to compare their mechanical properties and hemocompatibility with xenopericardial patches, routinely used in the clinical practice.

Material and Methods. Polymer matrices were electrospun from a polymer

blend contained 5% w/v PHBV (Sigma, St. Louis, MO, USA) and 10% w/v PCL (Sigma) dissolved in trichloromethane using a Nanon-01A setup (MECC CO) at a voltage of 20 kV, a solution feeding rate of 0.5 ml/h, a collector rotation speed of 200 rpm, and a tip-to-collector distance of 150 mm. A metal pin with a diameter of 8.0 mm was used as a collector. The matrix was cut lengthwise and peeled off when removing from the pin.

The surface of patches was primary modified with 1.6-hexamethylenediamine (labelled Amin1, Sigma-Aldrich, USA), or 4.7.10-trioxa-1.13-tridecanediamine (labelled Amin2, Sigma-Aldrich, USA) using the technique previously described in [6].

PHBV/PCL patches were modified by the following RGD-containing peptides: linear peptide RGDK (alanine-glycine-aspartic acid-lysine) referred as Pep1; linear peptide AhRGD (aminocaproic acid-alanine-glycine-aspartic acid) referred as Pep2; cyclic peptide c[RGDFK] (alanine-glycine-aspartic acid-phenylalanine-lysine) referred as Pep3. Modification and polymer bonding to the surface were evaluated as previously described in [6].

Mechanical properties of samples were evaluated under uniaxial tension with the universal testing machine series Z (Zwick/Roell, Germany) in accordance with the editorial rules of the ISO 270-75. The tensile strength was measured with the maximum tensile stress (MPa) at break and the maximally applied force, which represented the breaking load (Fmax, N). Elastic deformation was estimated with the relative elongation adjusted to the elongation at break (%) and Young's modulus (MPa) determined in the range of physiological loading (80-120 mmHg).

Commercially available xenopericardial KemPeriplas-Neo patches (NeoCor, LLC, RU) were used as the reference sample, since they are routinely used for CEA. Unmodified PHBV/PCL patches as well as the segments of human internal mammary artery excised during coronary artery bypass grafting were used as the benchmark samples. All patients provided written informed consent prior to surgery. Internal mammary artery samples were cut in the longitudinal axis.

The proportion of lysed blood cells was measured using fresh citrated blood. Positive and negative controls were saline and distilled water, respectively. The absorbance of the obtained supernatants was measured using the GENESYS 6 spectrophotometer (Thermo, Waltham, MA, USA) at the wavelength of 545 nm [9].

Platelet-rich plasma (PRP) was used to evaluate platelet aggregation. Platelet-poor plasma (PPP) was used for the calibration. Intact pure PRP was used as a positive control Samples were exposed to PRP for 3 min [4, 7, 14]. Spontaneous platelet activation was measured without any aggregation inducers. 0.025M CaCl2 was added to 250 μL PRP to restore the level of Ca2+ in citrated blood. Platelet aggregation was assessed using platelet aggregation analyser APACT 4004 (LA-BiTec, Germany).

Platelet adhesion and their deformation after contacting with polymeric patches as well as the surface structure was assessed using a S-3400N scanning electron microscope (Hitachi, Chiyoda, Japan) under high vacuum. "KemPeriplas-Neo" xenopericardial patches were assessed as the benchmark samples. Samples were produced according to the methodology previously described in [6]. Platelet adhesion was calculated using the platelet deformation index [7, 14]:

Deformation index = (number of type I platelets × 1 + number of type II platelets × 2 + number of type III platelets × 3 + number of type IV platelets × 4 + number of type V platelets × 5)/total platelet count. Types of platelets were assigned according to description presented in Table 1.

The normal distribution was estimated using the Kolmogorov–Smirnov test. The data are presented as a median and interquartile range [25th and 75th percentiles]. The Kruskal-Wallis test (ANNOVA) was used to compare three or more independent groups. A p value of <0.05 was considered statistically significant.

Results and Discussion. The presence of peptides on the polymer surface was confirmed using the Sakaguchi test [17, 18]. Covalent bonded RGD peptides were shown in light-yellow color even after the PHBV/PCL +RGD samples were washed. Light-yellow color of unmodified PHBV/PCL samples disappeared upon washing. Obtained data proved the efficiency of RGD peptide modification of of PHBV/PCL patches.

Scanning electron microscopy images confirmed the absence of the endothelial lining on the serosal surface of KemPeriplas-Neo patches. Though, native architectonics was preserved, including original relief with closely located tortuous collagen fibers resulting in the absence of pores (Fig. 1).

PHBV/PCL patches had highly porous structure with randomly arranged polymer fibers with a diameter of 350 nm to 4.0 μm. Pores of 5.1 up to 27.6 μm were formed due to fibers' chaotic interweaving (Fig. 1). The modification did not affect the architectonics of the PHBV/PCL + RGD patches that was similar to the original polymer patches (Fig. 1).

Biodegradable patches modified either with amines (Amin1 or Amin2) or RGD-containing peptides (Pep1, Pep2 or Pep3) demonstrated similar tensile properties. The differences were considered insignificant (p>0.05). Therefore, all patches modified with RGD peptides were assigned into the PHBCV /PCL + RGD group to compare them with the benchmark samples (xenopericardial patch, internal mammary artery, unmodified polymer patches).

Biological patches differed from human internal mammary artery (IMA) in tensile strength (Table 2). Tensile strength of the KemPeriplas-Neo patch and Fmax exceeded IMA by 4 and 16.7 times, respectively (p <0.05). However, RGD-modified patches and original PHBV/PCL patches demonstrated tensile strength and Fmax similar to human internal mammary artery (Table 2).

Young's modulus of KemPeriplas-Neo patches corresponded to that obtained for IMA, whereas polymer patches exceeded the last by 9 times (p <0.05). (Table 2, Fig. 2).

RGD modification resulted in a 3.25-fold decreased tensile strength and a 2-fold decreased Fmax exposed to the samples with similar thickness (p<0.05). None of the differences were found

Table 1

Platelet Deformation

Type	
I	Disc-shaped (no deformation)
II	Dendritic platelets with early pseudopodia sticking out
III	Spread dendritic platelets with intermediate pseudopodia sticking out; congregating
IV	Flat platelets with cytoplasm expanding among pseudopodia
V	Cytoplasm fully spreads; the shape of Pseudopodia cannot be seen clearly

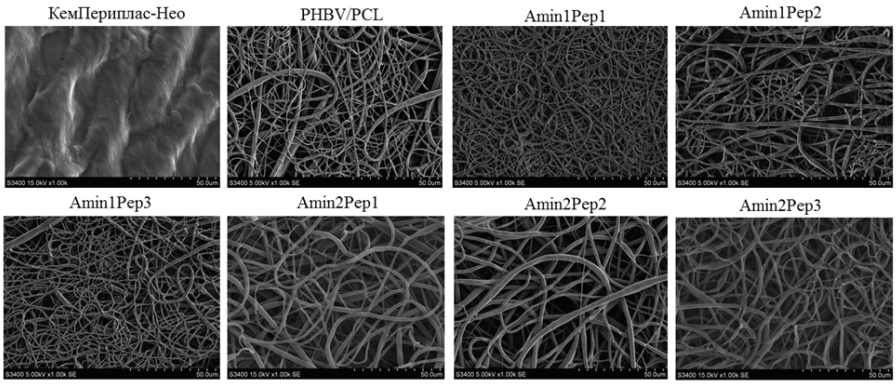

Fig. 1. Typical scanning electron microscopy images of biodegradable patches before and after RGD-peptides modification compared with KemPeriplas-Neo patches, ×1000 magnification

Table 2

Physical and mechanical properties of PHBV/PCL patches before and after RGD-peptide modification as compared to KemPeriplas-Neo xenopericardial patches and internal mammary artery, M (25-75%)

	Tensile Strength, MPa	Fmax, H	Elongation at Break, %	Young's modulus, MPa	Sample thickness, mm
PHBV/PCL	3.9 (2.88-4.5)	3.0 (2.59-3.3)	102.7 (79.37-106.3)*	21.8 (19.2-25.2)*•	0.4 (0.35-0.5)*
PHBV/PCL +RGD	1.2 (1.12-1.3)#•	1.3 (1.2-1.4)#•	102.6 (80.38-144.1)*	21.8 (20.15-23.9)*•	0.5 (0.49-0.5)*
Internal mammary artery	2.48 (1.36-3.25)	0.92 (0.59-1.72)	29.72 (23.51-39.62)	2.42 (1.87-3.19)	0.27 (0.24-0.3)
KemPeriplas-Neo	10.06 (9.12-21.38)*	15.4 (12.6-26.2)*	64.96 (61.08-72.6)*	1.11 (1.02-1.34)	0.69 (0.63-0.7)*

* – p<0.05 compared to IMA
# – p<0.05 compared to unmodified grafts
• – p<0.05 compared to KemPeriplas-Neo

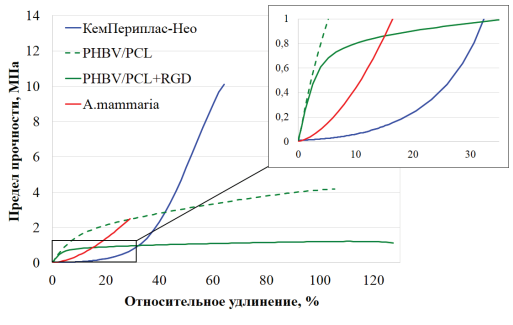

Fig. 2. Stress-strain curve of the study samples

between the elongation at break and Young's Modulus (Table 2, Fig. 2). Thus, RGD-modification resulted in decreased tensile strength, while its elongation properties remain the same.

The proportion of lysed red blood cells after contact with modified (Amin1 and Amin2) and unmodified PHBV/PCL patches was 0.36%; 0.72% and 0%, respectively (Table 3). Obtained data suggested high hemocompatibility of the study material [4]. Xenopericardial patches demonstrated a 2.12% red blood cell lysis that is generally considered acceptable [4]. However, the proportion the lysed RBCs was higher than that after the contact with modified patches (p <0.05). Significant differences were also observed between polymer patches modified with Amin1 and without modification. There were no statistically significant differences between patches modified with Amin2 and unmodified (p = 0.14). None significant differences were found between Amin1- and Amin2-modified PHBV/PCL patches (p=0.7).

The platelet aggregation maximum reliably increased after contacting with PHBV/PCL patches modified with Amin1 or Amin2 as compared to intact PRP with platelet aggregation activity of 15.02 (14.98; 17.72)%. (p <0.05). Unmodified patches and pure platelet-rich plasma demonstrated similar platelet aggregation (p=1.0), (Table 3).

KemPeriplas-Neo demonstrated the highest platelet aggregation (46.66% (21.06; 48.21), therewith a reliable increase in platelet aggregation was observed with respect to unmodified PHBV/PCL patches (p <0.05). Amin1- and Amin2-modified patches and xenopericardial patches did not differ in terms of platelet aggregation (p=0.05).

No doubt, RGD-modified PHBV/PCL and original PHBV/PCL patches had lower proportion of lysed red blood cells and superior platelet aggregation than KemPeriplas-Neo patches.

SEM images of nonwoven PHBV/PCL matrices after contact with platelets reported the presence of fibrin on their surfaces. Its presence complicated the assessment of platelet deformation (Fig. 3). Amin1Pep2- and Amin1Pep3-modified polymer patches had 1.2- and 1.4-times higher platelet deformation index than that of original PHBV/PCL patches (p<0.05). These patches had a higher number of adherent platelets mainly of type III-IV as compared to the other samples (Fig. 3). Upon contact with blood or being the result of modification, the modified and unmodified polymer patches demonstrated rather massive accumulations of adhered blood proteins. Platelet deformation indices of

Table 3

Platelet aggregation and platelet deformation after contacting with PHBV/PCL patches before and after RGD-modification in comparison with KemPeriplas-Neo xenopericardial patches

Sample	Proportion of lysed RBCs, %	Maximum Platelet Aggregation, %
	M (25-75%)	M (25-75%)
PHBV/PCL	0 (0-0)	17,06 (16,89-17,96) *
PHBV/PCL/Amin 1(RGD)	0,36 (0,36-0,36) *	23,74 (22,54-24,09)
PHBV/PCL/Amin 2(RGD)	0,72 (0-0,72) *	23,59 (21,44-24,35)
KemPeriplas-Neo	2,12 (0,9 -3,95)	46,66 (21,06-48,21)

* – p<0.05 compared to KemPeriplas-Neo

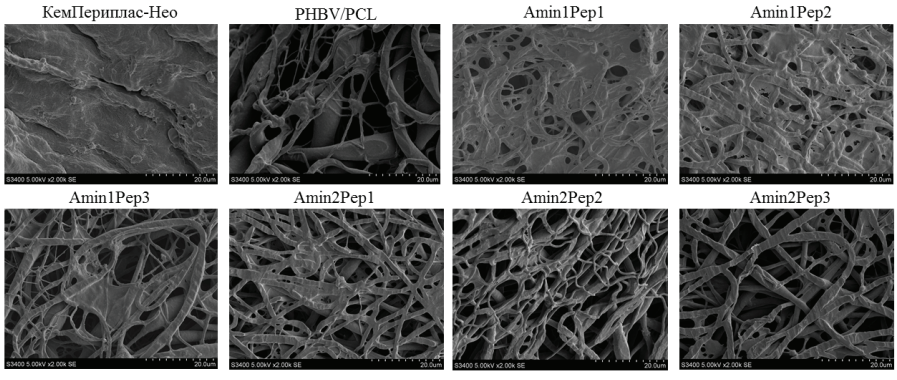

Fig. 3. Platelet adhesion on the surfaces of KemPeriplas-Neo patches and biodegradable PHBV/PCL patches with and without RGD modification, ×2000 magnification

Table 4

Platelet deformation index and the proportion of platelet types

Sample	Platelet Deformation Index. M (25-75%)
PHBV/PCL	2.7 (1.0-3.0)
PHBV/PCL/Amin1Pep1	2.5 (2.0-3.0)
PHBV/PCL/Amin1Pep2	3.31 (3.0-3.7)*
PHBV/PCL/Amin1Pep3	3.7 (3.4-4.5)*
PHBV/PCL/Amin2Pep1	2.6 (1.0-3.7)
PHBV/PCL/Amin2Pep2	1.3 (0.0-2.2)
PHBV/PCL/Amin2Pep3	2.9 (2.5-4.0)
KemPeriplas-Neo	2.33 (2.04; 3.13)

* – $p<0.05$ compared to unmodified PHBV/PCL patches

KemPeriplas-Neo and unmodified PHBV/PCL patches were almost similar. Amin2- and Amin1Pep1-modified polymer patches did not also differ significantly from them.

Conclusion. Biodegradable vascular patches have a highly porous surface that seems to be beneficial for vascular neotissue formation. RGD-modification of PHBV/PCL patches reduces their strength without affecting elongation at break. Nevertheless, RGD-modified and unmodified PHBV/PCL patches demonstrated tensile strength and Fmax similar to human internal mammary artery. However, Young's modulus of the polymer patches 9-times exceeded that of internal mammary artery.

RGD-modified and unmodified PHBV/PCL patches had few lysed red blood cells and mild platelet aggregation as compared to Kemperiplas-Neo patches. Obtained data suggested their high biocompatibility. The platelet deformation index increased greatly if 1.6-hexamethylenediamine was used for primary modification. Thus, the use of 4.7.10-trioxa-1.13-tridecanediamine as a linker for subsequent RGD-peptide modification of PHBV/PCL patches increased the biocompatibility of the implant.

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References

1. Севостьянова В.В., Головкин А.С., Антонова Л.В. и др. Модификация матриксов из поликапролактона сосудистым эндотелиальным фактором роста для потенциального применения в разработке тканеинженерных сосудистых графтов. Гены и клетки. 2015; 1(10):91–97. [SevostyanovaVV, Golovkin AS, Antonova LV et al. Modification of polycaprolactone scaffolds with vascular endothelial growth factors for potential application in development of tissue engineered vascular grafts. Genes & Cells. 2015; 1(10):91–97 (In Russ.).]

2. Антонова Л.В., Мухамадияров Р.А., Миронов А.В. и др. Оценка биосовместимости биодеградируемого сосудистого графта малого диаметра из полигидроксибутирата/валерата и поликапролактона: морфологическое исследование. Гены и клетки. 2015; 2(10):71–77. [Antonova LV, Mukhamadiyarov RA, Mironov AV et al. A morphological investigation of the polyhydroxybutyrate/valerate and polycaprolactone biodegradable small-diameter vascular graft biocompatibility. Genes & Cells. 2015; 2(10):71–77 (In Russ.).]

3. Texakalidis P, Giannopoulos S, Charisis N et al. A meta-analysis of randomized trials comparing bovine pericardium and other patch materials for carotid endarterectomy. J Vasc Surg. 2018; 68(4):1241–56. DOI: 10.1016/j.jvs.2018.07.023

4. Jolee Bartrom B.S. ASTM Hemolysis. NAMSA. 2008: 1–12.

5. Kudryavtseva VL, Stankevich KS, Gudima A et al. Atmospheric pressure plasma assisted immobilization of hyaluronic acid on tissue engineering PLA-based scaffolds and its effect on primary human macrophages. Materials and Design. 2017; 127:261–71. DOI: 10.1016/j.matdes.2017.04.079

6. Antonova LV, Silnikov VN, Sevostyanova VV et al. Biocompatibility of Small-Diameter Vascular Grafts in Different Modes of RGD Modification. Polymers. 2019; 11(1):174. DOI: 10.3390/polym11010174

7. Biological evaluation of medical devices. Part 4: Selection of tests for interaction with blood. NSAI standards. EN ISO 10993-4:2017

8. Antonova LV, Sevostyanova VV, Mironov AV et al. In situ vascular tissue remodeling using biodegradable tubular scaffolds with incorporated growth factors and chemoattractant molecules. Complex Issues of Cardiovascular Diseases. 2018; 7(2): 25–36. DOI: 10.17802/2306-1278-2018-7-2-25-36

9. Shen X, Su F, Dong J et al. In vitro biocompatibility evaluation of bioresorbable copolymers prepared from L-lactide, 1, 3-trimethylene carbonate, and glycolide for cardiovascular applications. Journal of Biomaterials Science, Polymer Edition. 2015; 26(8):497–514. DOI: 10.1080/09205063.2015.1030992

10. Bonati LH, Dobson J, Featherstone RL et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the international carotid stenting study (ICSS) randomised trial. Lancet. 2015; 385(9967):529–38. DOI: 10.1016/S0140-6736(14)61184-3

11. Cho S-W, Jeon O, Lim JE et al. Preliminary experience with tissue engineering of a venous vascular patch by using bone marrow–derived cells and a hybrid biodegradable polymer scaffold. J Vasc Surg. 2006; 44(6):1329–40. DOI: 10.1016/j.jvs.2006.07.032

12. Mettler BA, Sales VL, Stucken CL et al. Stem cell–derived, tissue-engineered pulmonary artery augmentation patches in vivo. Ann Thorac Surg. 2008; 86(1):132–41. DOI: 10.1016/j.athoracsur.2008.02.074

13. Abbott AL, Paraskevas KI, Kakkos SK et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. Stroke. 2015; 46(11): 3288-301. DOI: 10.1161/STROKEAHA.115.003390

14. Kundu B, Schlimp CJ, Nürnberger S et al. Thromboelastometric and platelet responses to silk biomaterials. Sci Rep. 2014; 4:4945. DOI: 10.1038/srep04945

15. Radke D, Jia W, Sharma D et al. Tissue engineering at the blood-contacting surface: a review of challenges and strategies in vascular graft development. Adv Healthc Mater. 2018; 7(15): e1701461. DOI: 10.1002/adhm.201701461

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REMOTE RESULTS OF SURGICAL TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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The article is devoted to the problem of surgical treatment of primary hyperparathyroidism. The paper presents a comparison of the results of surgical treatment performed from a standard access with a mandatory revision of 4 parathyroid glands and a gentle method of small access with the removal of the affected parathyroid glands.

The obtained results showed the promise of sparing approach to the treatment of PGPT caused by adenoma of the parathyroid glands was.

Keywords: primary hyperparathyroidism, parathyroidism, hyperplasia, adenoma, low access, quality of life assessment.

Relevance. Primary hyperparathyroidism (PGPT) - primary pathology parathyroid glands, characterized by excessive secretion of parathyroid hormone. Since the latter is a regulator of mineral exchange in the pathological process involved almost all organs and systems, in turn, generates the clinical picture diverse and difficulties in the differential diagnosis of the disease. With scant clinical symptoms in the early stages and the presence of asymptomatic forms of the course, PGPT in most cases detected by chance, proving the importance of minimum endocrinological vigilance in respect of non-specific complaints of patients: to fatigue, weakness, depression, etc. With the development of studies and laboratory methods in routine practice introduction biochemical screening tests on blood ionized calcium levels as the primary marker of the disease, there is a jump increase PGPT initially diagnosed cases [1].

Today, surgery with the classic traditional access by Kocher is the "gold standard" treatment for patients with PGPT [2], which provides a full audit of all parathyroid glands.

Along with this, there are reports about the possibility of using a small access by removing adenomas parathyroid glands without revision others [3,4]. But among modern writers there are opponents who report high relapse rate.

Purpose. To evaluate the effectiveness of surgical treatment PGPT based on the analysis results of the nearest and remotest from the standard and parathyroidectomy small accesses.

Materials and methods. From 2009 to 2017 Burdenko Clinic of Surgery №1 based of the First Moscow State Medical University named after I.M. Sechenov. has been on the treatment of 418 patients PGPT. The selection criteria in this paper is a must histological confirmation of adenoma parathyroid glands. The current study included 370 patients with adenomas parathyroid glands. Patients with hyperplasia (n = 37) and parathyroid glands cancer (n = 11) were excluded.

The study consisted of a study of disease histories, history and primary examination data, laboratory-instrumental examination methods data, operation protocols and histological study results, and postoperative course data.

To study the long-term results of surgical treatment, 370 patients with PGPT were divided into 2 groups:

- Group 1 (GR1) - Patients who received surgical treatment until 2012, op-

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