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Electrospinning for the design of medical supplies

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ABSTRACT

In this review, various achievements in the field of development of tissue-engineered scaffolds with the electrospinning approach were observed. Through the appropriate selection of electrospinning parameters, such as solution viscosity, the type of solvent, voltage, the distance between a tip and a collector etc., scaffolds with a high degree of porosity and pore size applicable for optimal cell infiltration can be obtained. These tissue-like materials can be produced from both synthetic and natural polymers and their mixtures. Based on the characteristics specific for the desirable tissue – vascular, bone or cardiac – materials providing the required mechanical properties, architecture, degradation kinetics and biocompatibility are selected for scaffold synthesis. In different studies, electrospun fibers were modified by adding biologically active agents or nanoparticles. This article also describes the particularities of the extracellular matrix of different tissues and approaches used for specific tissue imitation. Repopulation of the matrices with autologous cells before transplantation is the most commonly used method to improve the biocompatibility of the scaffold and the recipient.

Key words: tissue engineering, nanofibers, electrospinning, scaffolds, extracellular matrix, implants.

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Электроспиннинг для дизайна материалов медицинского назначения

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РЕЗЮМЕ

Рассмотрены достижения в области получения скаффолдов для тканевой инженерии методом электроспиннинга. При правильном подборе параметров электроспиннинга, таких как вязкость раствора, тип растворителя, напряжение, расстояние от иглы до коллектора и т.д., можно получить материалы с высокой степенью пористости и необходимым размером пор, подходящим для оптимальной инфильтрации клеток. Данные тканеподобные материалы можно получать как из синтетических и природных полимеров, так и их смесей. Исходя из свойств, присущих конкретной ткани – сосудистой, костной, сердечной и т.д., подбираются материалы для синтеза скаффолда, обеспечивающие необходимые механические характеристики, структуру, скорость деградации и биосовместимость. Многие исследователи функционализировали волокна путем добавления биологически активных веществ или наночастиц. В обзоре также рассмотрены особенности

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внеклеточного матрикса различных видов тканей и подходы, которые применяются для имитации ткани в каждом конкретном случае. Заселение скаффолдов клетками перед трансплантацией является наиболее распространенным подходом для повышения биосовместимости скаффолда с тканями реципиента.

Ключевые слова: тканевая инженерия, нановолокна, электроспиннинг, скаффолды, внеклеточный матрикс, имплантаты.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

It is known that some organs and tissues of the human body are able to self-regenerate. For conditions when self-regeneration is limited, tissue-engineering approaches have been developed to create artificial tissues for reparation or organ replacement [1–3]. The electrospinning method is a new direction in this field, which makes it possible to create an implantable scaffold (prosthesis) with the required physicochemical characteristics [4]. The resulting porous structure facilitates active migration of cells into the wall of the prosthesis, formation both the supplying blood system and the internal endothelial layer. The electrospun scaffold should have a structure similar to the extracellular matrix of the replaced tissue to provide conditions for cell adhesion, growth and proliferation [5, 6]. Along with this, the implantable prosthesis should also have biocompatibility, a suitable pore size for cell infiltration and mechanical integrity [7, 8]. As a rule, such prostheses are made from biodegradable materials, which makes them a temporary supporting structure for the period of cell growth and tissue regeneration. The rate of degradation of the scaffold should coincide with the rate of new tissue formation.

ELECTROSPINNING PROCESS. EQUIPMENT AND MATERIALS

The basic elements of the electrospinning setup are a needle, through which a polymer solution is administered, and a collector, designed to carry the incoming polymer. These elements are combined into one electrical circuit. As the voltage increases, the surface tension forces of the polymer solution are overcome at the end of the needle, resulting in the formation of a Taylor cone – a tapered drop of polymer [9, 10]. As the voltage becomes sufficient, a polymer jet rises from the top of the cone in the direction of the collector, the diameter of which depends on many conditions. In the air, a part of the solvent evaporates and the jet splits, as a result of which a pure polymer is deposited on the collector in the form of randomly or directionally laid fibers with sizes in the nano- to micrometer range. The obtained material has the form of a thin, fibrous, porous soft fabric or thin elastic coating.

Structurally, the electrospinning setups are similar, the differences are associated only with the design (horizontal, vertical, etc.). In addition, setups with double electrospinning can be equipped with elements that control the formation of threads and fabric materials [11]. An interesting technology is the coaxial electrospinning, which allows to obtain combined (like a braided wire) threads [12, 13].

The electrospinning process is influenced both by the properties of the solution (viscosity, electrical conductivity, polymer concentration, surface tension) and controlled variables: the rate of the solution feed or polymer dissolution, the amplitude of the electric voltage, the distance between the needle and the collector, temperature, and humidity [14, 15].

The viscosity, electrical conductivity and surface tension of polymer solutions depend on the concentration and properties of the polymer and solvent used. Typically, the viscosity of solutions in electrospinning processes is in the range of 1–20 poise (Ps) and depends on the concentration (usually in the range of 10–30%) and the molecular weight of the polymer [16, 17]. Optimum solvents should have low viscosity and a low boiling point (for example, DCM, THF, DMF, water, methanol, hexafluoroisopropanol, etc.); solvent mixtures are also used [18–20]. The surface tension of the solutions is also determined by the nature of the solvent and the polymer (usually about 10^2–10^3 dyne / cm), although in practice this factor is rarely controlled.

The main controlled parameters, such as the polymer feed rate (from 0.1 to 10 ml/h), the voltage value (from 1 kV to 60 kV), the distance between the needle and the collector (from 10 cm to 50 cm), the diameter of the nee-

dle (18–27G), and the speed of rotation of the receiving collector (0–3000 rpm), are determined experimentally. In the vast majority of cases, the temperature and humidity in an electrospinning installation are not considered.

Electrospinning technology is suitable for manufacturing polymer filaments, tangles and films from soluble or molten polymers and allows to create fibrous materials with specified spatial characteristics (diameter, spatial orientation and adhesion of fibers, porosity, the presence of channels for cell proliferation). Thanks to this, materials for cell and tissue engineering are created and studied: various scaffolds for nerve tissue, skin, bone tissue, etc.; dressings; drug delivery vehicles [21–23].

BIODEGRADABLE VASCULAR GRAFT PRODUCTION

The ability to combine the advantages of synthetic and natural polymers via electrospinning makes this method particularly attractive for the design of vascular grafts requiring high mechanical tensile strength and sufficient elasticity (Young's modulus) [24]. In addition, the inclusion of natural polymers with a large number of cell binding sites in the scaffold can contribute to the formation of a continuous monolayer of epithelial cells in the lumen and the proliferation of other types of cells in the graft matrix. The electrospinning method provides precise control of the composition, size and direction of the fibers, which affects the porosity of the material, pore size distribution, and scaffold architecture [25]. It is important to note that directed nanofibers can be used to orient cells in a certain direction to provide the necessary anisotropy that occurs in some organs, including blood vessels [26].

A group of authors [27] obtained tubular scaffolds from a copolymer of poly-L-lactide and poly-ε-caprolactone with a diameter of 3 mm, which were implanted into rabbits in the lower superficial epigastric veins for a period of 7 weeks. It was revealed that the frames withstood the surgical process, retained structural integrity and patency throughout the observation period. In addition, endothelial cells obtained from the human coronary artery were evenly distributed and spread well throughout the carcass cavity within 10 days after application.

Vascular grafts obtained from a solution of recombinant human tropoelastin and polycaprolactone were chosen in [28] to simulate the mechanical properties of the human thoracic artery (elastic modulus, ductility, permeability, and rupture pressure). Cell adhesion and proliferation were investigated using human umbilical vein endothelial cells. The cell-free framework was implanted into rabbits and removed one month later, followed by a study of the mechanical characteristics. In the case of transplants of elastin / polycaprolactone composition, increased vascular compatibility and endothelization were observed with reduced platelet attachment compared with transplants without elastin. The addition of tropoelastin significantly improved cell adhesion and proliferation.

Polyurethane–urea grafts were implanted in rat aorta for up to 24 weeks [29]. The interior of the grafts was coated with a non-thrombogenic 2-methacryloyloxyethyl phosphorylcholine copolymer, which resulted in reduced platelet adhesion and improved patency compared to uncoated grafts. The mechanical properties of the grafts were also compatible with those of native arteries. Numerous *in vivo* experiments using composite bilayer polyurethane–urea grafts with applied muscle stem cells of rats, introduced into their aorta [30, 31], showed higher throughput for grafts with applied cells compared to grafts without cells.

Vascular grafts from biodegradable polyurethane were implanted in rat abdominal aorta for the periods of 7 days, 1 month, 6 months, and 12 months [32]. A comparison was made with commercially available ePTFE grafts. In all cases, rejection of the implants by the body or their degradation was not observed. With a long implantation period, the implant patency was 100%. The implant removed after 12 months remained mechanically stable and was fully integrated into the surrounding tissue.

The emulsion electrospinning method was used to make heparin-filled poly (L-lactide-co-caprolactone) nanofibers (PLCL) used as a stent coating. In a rabbit model, it was found that a stent coated in such a way effectively separated the aneurysm from the bloodstream [33]. In another work, Wang et al. [34] mixed vascular endothelial growth factor (VEGF) with heparin to accelerate endothelialization and loaded the resulting mixture into the core of PLCL nanofibers. Isolation of heparin and VEGF from PLCL-Hep-VEGF scaffolds lasted more than 30 days, which increased the proliferation of porcine iliac endothelial cells on the stent.

Feng et al. obtained coxial electrospinning stents coated with PLCL nanofibers filled with heparin and calcium rosuvastatin [35]. The coated stent showed increased anticoagulant ability, and the endothelial cells proliferated well on the coated stent due to the prolonged release of rosuvastatin calcium and heparin (more than 45 days) from PLCL coaxial nanofibers.

In a similar work by Chen et al., heparin and VEGF were encapsulated in PLCL nanofibers by emulsion electrospinning to create vascular grafts [36]. Heparin and VEGF showed a sustained release for 29 days, which gave the studied transplant good anticoagulation ability and led to the growth of endothelium.

Similarly, platelet-rich growth factor (PRGF) at a

concentration of 20 mg / ml was added to the PLCL to prepare an electrospinning solution from which a tubular graft with a fiber diameter of 4 nm was prepared. This approach facilitated rapid penetration of cells into the graft and the growth of endothelium [37].

A group of authors [38] investigated the release of tritium-labeled paclitaxel (3H-PTX) from matrices designed to coat vascular stents and obtained by electrospinning from solutions of polycaprolactone (PCL) with paclitaxel (PTX) and human serum albumin (HSA) in hexafluoroisoropropanol (HFIP). It was shown that 3D matrices can completely release PTX with virtually no weight loss. Approximately 27% of PTX was released on the first day, another 8% – in the next 26 days. Given the toxicity of PTX and the rate of diffusion through the arterial wall, it is expected that the minimum cytostatic dose of the drug in the artery wall will be maintained for at least three months.

MATERIALS FOR SKIN REGENERATION AND WOUND HEALING

High porosity, small pore size and large surface area of electrospinning coating materials make them suitable for wound dressings, where they provide effective protection against bacterial infection of the damaged skin surface and the ability to drain wound fluids and gases through the dressing. Electrospinning coatings can also work as platforms for the delivery of biologically active substances, such as antimicrobial agents to fight infections and agents to improve wound healing [39, 40].

The main component of the extracellular matrix of the skin is collagen fibers that provide mechanical and structural integrity of the skin and have diameters in the range of 50–500 nm [41, 42]. Therefore, any material for skin regeneration should also have a fiber diameter in the nanometer range. Among natural polymers, collagen, fibroin, gelatin, and chitosan / chitin are often used for this purpose. Thus, a group of authors [43] obtained collagen nanofibers with a diameter of 100–1200 nm by electrospinning. The mechanical properties of the collagen matrix were comparable to those for commercially available materials for regeneration of damaged tissues. In experiments on rats, the matrices obtained were highly effective in the treatment of wounds at early stages.

Fibroin secreted from silkworm cocoons is characterized by excellent biocompatibility, high strength, slow degradation, and minimal inflammatory response [44]. However, the material formed during electrospinning has a small pore size, which prevents proper cell infiltration. A group of researchers obtained fibers from a mixture of silk fibroin and polyethylene oxide with the simultaneous deposition of NaCl crystals during electrospinning [45]. Good adhesion and infiltration of 3T3 fibroblasts on the matrix were observed. In rat wound treatment experiments, this scaffold closed wounds faster and degraded more efficiently than the commercially available MatriDerm® regenerative material.

Synthetic polymers (polyglycolide, polylactide, poloxamer, polycaprolactone, polystyrene, polyvinylpyrrolidone, etc.) are also used for skin regeneration. A group of authors [46] conducted a comparative study of fibers obtained from polycaprolactone, a mixture of chitosan / polyethylene oxide and gelatin by electrospinning their solutions in acetic acid. In *in vitro* tests, the material of the chitosan / polyethylene oxide composition was characterized by low cell adhesion and proliferation, while during the *in vivo* study in rats it had the greatest influence on the treatment process, effectively blocking wound contraction and enhancing its epithelization. The polycaprolactone scaffold also performed poorly in *in vitro* experiments, but acted well as a physical barrier against wound contraction. When using gelatin, the best *in vitro* results were observed, while the *in vivo* behavior was comparable to the control group (wound regeneration without the use of a scaffold).

The method of electrospinning of a polyurethane solution produced nanofibers with an average diameter of 250–300 nm [47]. A study on the treatment of wounds using a polyurethane membrane was carried out on guinea pigs; the control group received treatment with the commercial product Tegaderm ™. Good, uniform adhesion of the nanofiber membrane to the wound surface was observed without accumulation of fluid. At the same time, its toxic effects or permeability to exogenous microorganisms were not revealed.

El-Aassar et al. [48] developed electrospinning composite wound coatings containing polyvinyl alcohol (PVA) / Pluronic F127 (Plur) / polyethyleneimine (PEI) and titanium dioxide nanoparticles (TiO2 NP). In this study, TiO2 nanoparticles were used as an antimicrobial agent. Antibacterial tests showed that the fabricated PVA-Plur-PEI / TiO2 nanofibers exhibited better bactericidal activity than PVA-Plur-PEI nanofibers.

Lv et al. [49] reported a polycaprolactone (PCL)/ gelatin electrospinning framework containing silica-based bioceramic particles (Nagelschmidtite, NAGEL, Ca7P2Si2O16) for wound healing. Using the joint electrospinning process, NAGEL bioceramic particles were uniformly distributed in PCL / gelatin fibers, and when the framework was destroyed, silicon-containing ions (silicates) were gradually released from the fiber. Cell tests (for example, umbilical vein endothelial cells (HUVECs) and human keratinocytes (HaCaTs)) showed that scaffolds can significantly contribute to cell adhesion, proliferation and migration. The wound sites reconstructed by these scaffolds showed the desired healing

results in terms of angiogenesis, collagen deposition, re-epithelialization, and inhibition of the inflammatory response.

MATERIALS FOR BONE TISSUE, TENDON AND LIGAMENT REPARATION

The key points when using scaffolds obtained by electrospinning for bone tissue regeneration are the presence of a system of interconnected pores, proper mechanical properties, a controlled degradation rate, and fiber size corresponding to the structure of the extracellular matrix of the bone [50]. The extracellular matrix of the bone is a nanocomposite consisting of collagen fibers, inorganic nanocrystallites, and growth factors [51].

The possibility of obtaining scaffolds for bone tissue regeneration from polycaprolactone was studied [52]. The polycaprolactone nanofiber matrix obtained by electrospinning from a chloroform solution consisted of randomly oriented fibers with diameters ranging from 100 nm to 5 μm.

Scaffolds coated with rat bone marrow mesenchymal stem cells were cultured with osteogenic additives in the bioreactor for 4 weeks with the following implantation in the omentum. After removal, the scaffolds retained their original size and shape, were stiff and looked like a bone. Throughout the matrix, the formation of cells and extracellular matrix was observed with the formation of tissue similar to that of the bone.

Hydroxyapatite (HA), as the main mineral component of the bone matrix, is widely used in medicine for bone tissue reconstruction [53], but its use is limited by its inherent high fragility. One of the solutions to this problem is to obtain composite materials with polymers [54–56]. Thus, a nanofiber network of collagen and hydroxyapatite (HA content of about 20%) was obtained by electrospinning a solution of their nanocomposite [57]. The biocompatibility of nanofibers was investigated using mouse osteoblastic cells. The cells were viable and showed good growth parameters both in the case of collagen nanofibers and in the case of nanocomposite.

Scaffolds made from silk fibroin fibers containing human recombinant bone morphogenetic protein (BMP-2) and / or hydroxyapatite nanoparticles obtained by electrospinning were used to form bone tissue *in vitro* from human mesenchymal bone marrow stem cells [58]. BMP-2 underwent the process of electrospinning in the aquatic environment and retained bioactivity. Cells were cultured on scaffolds for 31 days in an osteogenic environment. The scaffold supported the processes of growth and osteogenic differentiation of cells. Co-application of BMP-2 and hydroxyapatite onto the fibers resulted in the highest levels of calcium deposition and increased the levels of BMP-2 transcription compared to other systems. However, BMP-2 has disadvantages associated with rapid enzymatic hydrolysis, undesired bone growth, immune responses, and high cost [59]. Recently, peptides derived from BMP-2 [60], which have a positive effect on osteogenic differentiation of stem cells and bone formation in defects [61], have attracted great attention as alternative biologically active molecules.

Ye et al. [62] developed nanoscale 3D frameworks of nano-hydroxyapatite / PLLA / gelatin (nHA / PLA / GEL) with immobilized on them derivatives of BMP-2 peptides, capable of delayed release. *In vitro* studies have shown that nHA / PLA / GEL-PEP scaffolds stimulate bone mesenchymal stem cell alkaline phosphatase activity (BMSCs) and gene expression associated with osteogenic differentiation. In addition, in an *in vivo* model, this scaffold promoted bone formation in defects of rat cranial bones. Hence, it is stated that this framework has great potential for repairing bone defects [62].

Native ligaments and tendons have a wide range of mechanical properties. Therefore, for the successful creation of tissues replacing these damaged structures, the mechanical properties of the scaffold play a crucial role [63]. Hybrid nano-microfiber scaffolds were developed by electrospinning a solution of polylactide-co-glycolide onto an already prepared scaffold woven from fibers of the same polymer [64]. Pig bone marrow stromal cells were applied to hybrid scaffolds, and woven scaffolds without nanofibers, onto which cells suspended in a fibrin gel were applied, were used as a control group. Indicators, such as cell adhesion, proliferation, and expression of type I collagen and decorin, were higher for the hybrid scaffold group. A limitation in the use of such nano-microfiber scaffolds is their mechanical properties, which do not correspond to those characteristic of native tendons and ligaments.

MATERIALS FOR CARDIAC TISSUE REGENERATION

Tissue engineering and cell therapy are now seen as alternative therapeutic approaches to stimulate the regeneration of infarcted tissue. Cardiac scaffolds can replace or support the function of the heart muscle with the possibility of providing cell and drug therapy after myocardial infarction [65, 66]. Both synthetic and natural polymers are used to produce heart scaffolds.

In [67], the production of matrices of different composition by electrospinning was described: poly-L-lactide; 75% polylactide-co-glycolide (lactide / glycolide = 10 / 90) mixed with 25% poly-L-lactide; 85% polylactide-co-glycolide (lactide / glycolide = 75 / 25) mixed with 15% copolymer of polyethylene glycol with poly-D, L-lactide. During the cultivation of cardiomy-

ocytes on the obtained matrices, it was revealed that cardiomyocytes were sensitive to the composition of materials with a preference for relatively hydrophobic surfaces. The density of cardiomyocytes on hydrophilic and rapidly decomposing surfaces was lower. Matrices of poly-L-lactide showed the best parameters for cell adhesion.

The work [68] describes the preparation of composite fibers, the core of which consists of polyglycerol sebacate, and the outer part – of fibrinogen. The fibers had an average diameter of 1076 ± 212 nm. It was shown that the obtained fibers had a Young's modulus comparable to that of the native heart muscle. Neonatal cardiomyocytes that were cultured on these scaffolds showed normal expression of specific proteins.

A number of scaffolds with directed and randomly oriented fibers were obtained by electrospinning from a mixture of polyglycerol sebacate / gelatin with different ratios of components [69]. The adhesion, proliferation, and differentiation of fibroblasts and cardiomyocytes were influenced by the chemical composition and stiffness of the scaffold, and the alignment and organization of cells was influenced by the directed or random arrangement of the fibers. Scaffolds with directional fibers containing 33% polyglycerol sebacate allowed to achieve optimal synchronous contractions of cardiomyocytes with significantly improved cell organization in given directions.

Some conductive and biocompatible polymers, such as polyaniline and polypyrrole, have been used to make conductive cardiac scaffolds. In particular, a scaffold was made from directional conductive fibers of polyaniline and a copolymer of polylactic and polyglycolic acids [70]. Cells cultured on fibers formed clusters, and all cardiomyocytes within the cluster contracted synchronously, which implies a fully developed intercellular connection.

Another approach to improve the physical and biological properties of a scaffold is to coat its surface with nanofibers. In some cases, scaffolds coated with electrospinning nanofibers, after removing cells from the surface of the scaffold, showed better mechanical properties and kinetics of degradation than before modification [71]. For example, a group of researchers conducted an experiment to obtain hybrid leaflets of the heart valve with a biomatrix / polymer composition [72]. The leaflets of the pig's heart valve were purified from cells and coated with a mixture of fibroblast / chitosan / poly-4-hydroxybutyrate growth factors by electrospinning. Further, the leaflets were seeded with rat mesenchymal stem cells and cultured for 14 days. As a result, the hybrid scaffold showed good cell population and a significant increase in their mass, the formation of 4-hydroxyproline and collagen, and also had mechanical properties comparable to those of the native valve.

In a recent work [73], a fiber frame of a polycarbonate–polyurethane valve was developed by electrospinning, which imitates the shape of a native heart valve. According to the authors, the cell-free, slowly collapsing elastomeric valve implant should be gradually populated by endogenous cells with the formation of new valve tissue inside the heart. Orthotopic implants in the form of a pulmonary valve in sheep showed stable functionality for up to 12 months, while the polymer implant was gradually replaced by layered collagen and an elastic matrix as the cells resorbed.

As for medical bioresistant implants, for materials obtained by electrospinning, the scope has not yet been determined. For implants, especially artificial heart valves (AHV), increased operational requirements are imposed: long-term elasticity, wear resistance, biostability, not to mention hemocompatibility and resistance to calcification. To date, biological AHV with moving elements from an animal pericardium demonstrate the greatest success in practice, although in this case it is also difficult to achieve long trouble-free lifetime of the valve (usually no more than 10 years) [74]. Artificial biomimetic heart valves with a movable base made of artificial materials (polymers, such as PTFE, polyurethanes, etc.) are currently considered promising, but need more in-depth study than the already known mechanical or biological ones [74]. Therefore, the technology of electrospinning should be rather considered as an auxiliary method in the production of combined biostable materials. For example, electrospinning microfibers can be used as a reinforcing component when creating the appropriate composite (valve prosthesis, vessel, graft) with an impregnated polymer matrix or to modify the surface layer of the product with nanofibrils for better epithelization where necessary.

CONCLUSION

The task of tissue engineering is to restore the functions of damaged tissue. The electrospinning method allows to obtain polymer scaffolds for the needs in this area. By varying the parameters of electrospinning, it is possible to obtain materials with the required fiber diameter, pore size and porosity. In addition, electrospinning allows to obtain fibers from various polymers, both of synthetic and natural origin. This technology allows to combine the advantages of synthetic and natural polymers to obtain biocompatible scaffolds with mechanical properties corresponding to native tissues. The selection of conditions and materials for electrospinning is carried out depending on the properties of the extracellular matrix of the replaced tissue. However, today, the number

of *in vivo* studies for tissue-engineering materials obtained by electrospinning is still insufficient to talk about the operational flexibility of this technology.

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Kretov E.I. – final approval of the manuscript for publication. Zapolotsky E.N. – conception and design, drafting of the manuscript. Tarkova A.R. – final approval of the manuscript for publication. Prokhorikhin A.A. – critical revision for important intellectual content. Boykov A.A. – collection, analysis and interpretation of data. Malaev D.U. – collection, analysis and interpretation of data.

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