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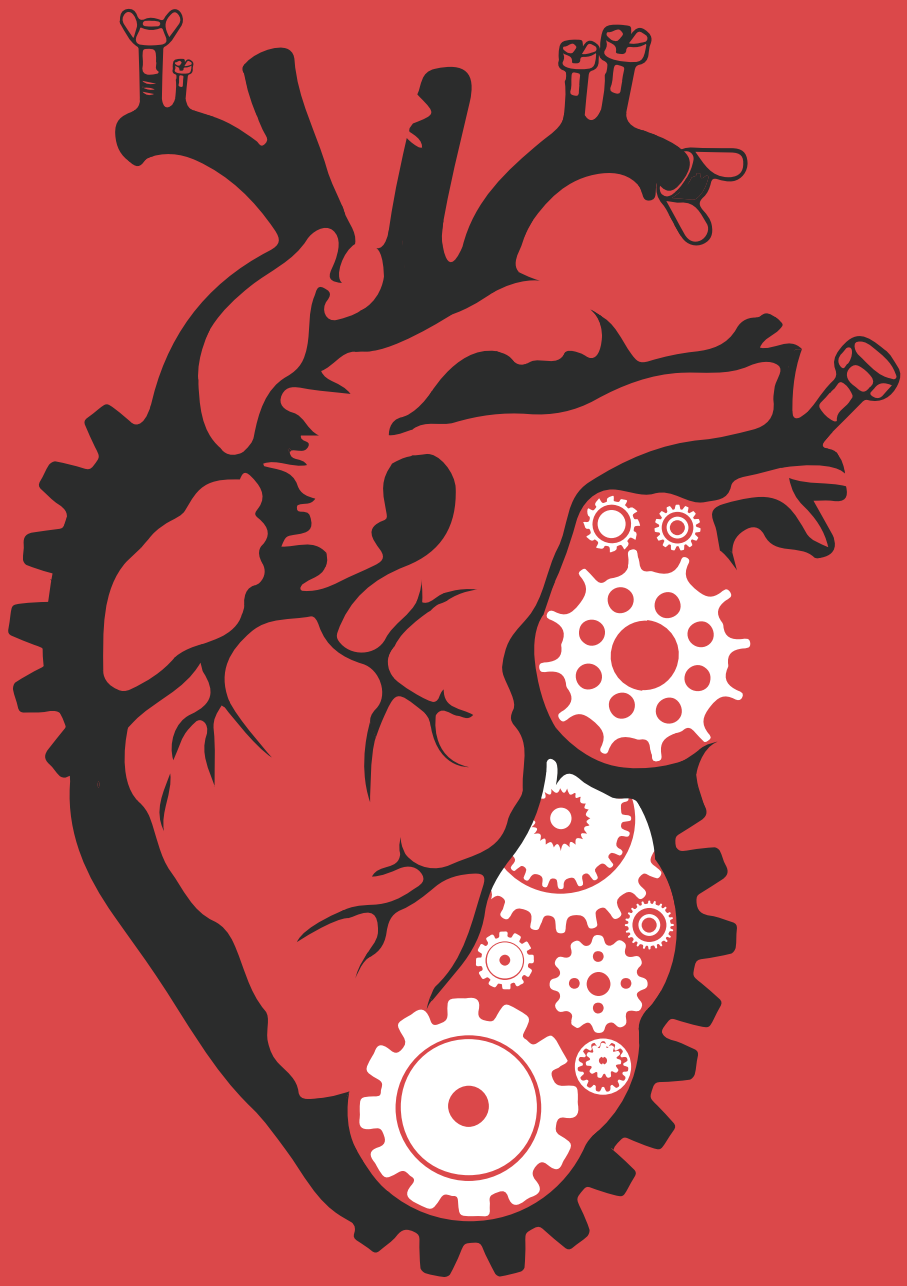

BIOMATERIALS REVIEW

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СОДЕРЖАНИЕ

BIOMATERIALS ARE AN IMPORTANT AREA OF BIOMEDICAL TECHNOLOGIES

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The review describes the use of biomaterials (polymeric biomaterials in particular) in the development of medical and biological products and devices, such as implants and endoprostheses; components of bioactive and pharmaceutical agents; carriers for bioengineering applications; sorbent agents and membrane systems used for the purification and separation of biological media; artificial biocatalysts, and general purpose biodegradable products. This review is provided with a short reference list of relevant monographs and reviews predominantly by Russian authors.

Keywords: artificial materials, biomaterials, polymer, endoprosthesis, implant, biodegradation

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БИОМАТЕРИАЛЫ — ВАЖНОЕ НАПРАВЛЕНИЕ БИОМЕДИЦИНСКИХ ТЕХНОЛОГИЙ

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Обзор посвящен использованию биоматериалов, преимущественно полимерных, для создания изделий и препаратов медико-биологического назначения — имплантатов и эндопротезов; компонентов биологически активных и лекарственных препаратов; носителей, предназначенных для использования в биоинженерных методах; сорбентов и мембранных систем, применяемых для очистки и разделения биологических сред; искусственных биокатализаторов; биодеградируемых изделий общего назначения. Обзор снабжен кратким списком литературы, состоящим в основном из монографий и некоторых обзоров в данной области, изданных преимущественно на русском языке.

Ключевые слова: искусственные материалы, биоматериалы, полимер, эндопротез, имплантат, биодеградация

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In the international literature, materials that interact with living tissues, organs and organisms are commonly referred to as “biomaterials”. The methods of their production, research and application have been actively evolving in recent decades. To a large extent they determine the current level of development of such areas of knowledge as medical science, pharmaceutics, cosmetics, biotechnology, agriculture, and food industry (life sciences and technologies).

There are scientific journals on biomaterials that generally have a very high impact factor, namely *Biomaterials, International Journal of Biomaterials, International Journal of Polymeric Materials and Polymeric Biomaterials, Journal of Biomaterials, Journal of Biomaterials Science, Journal of Biomedical Materials Research, Journal of Biotechnology and Biomaterials, Journal of Controlled Release, Advances in Materials Science and Engineering, Journal of Functional Biomaterials, Journal of Materials Science: Materials in Medicine*, and others. A number of international encyclopedias and reference books have been published covering various issues related to biomaterials, such as [1, 2]. A high-quality textbook *Biomaterials Science* underwent 3 editions (in 1996, 2004, and 2013) and is recommended for the US universities [3]. The following international and national societies work actively to develop this area of science, conduct international conferences and congresses, and publish their own journals: International Society for Biomedical Polymers and Polymeric Biomaterials, International Union of Societies for Biomaterials Science and Engineering, International Society of Controlled Release, Society for Biomaterials (US), European Society for Biomaterials, Canadian Biomaterials Society, UK Society for Biomaterials, and others. The size of the global biomaterials market has become quite noticeable (see the table below).

The development, research and manufacturing of medical and biological supplies and products are regulated by GMP (Good Manufacture Practice) standards. Despite the fact that metals, carbons, inorganics and composites are important members of the biomaterials family, polymers are particularly special as it is possible to obtain polymer-based articles and agents that not only have the required physical and technical characteristics, but also can swell and dissolve in water, which is unnatural for other groups of biomaterials. As a rule, polymeric biomaterials are produced in relatively small quantities, but they are significantly superior to other groups of the polymeric materials in terms of range and diversity of properties [4].

The field of biomaterials is a prominent interdisciplinary field where the achievements of chemistry, physics, medicine, biotechnology, metallurgy, and electronics are applied. This

The size of the global market of biomaterials and biomaterial-based products

Object	Market size. $ bln	Annual growth. %	Source
Biomaterials	62.1 (2015) 115.2 (2020)	+10.3	[ResearchMarket. 2016] [MarketInteligence. 2016]
Implants	70.8 (2015) 115.8 (2020)	+10.3	[Allied Market Research. 2016]
Materials for treatment of wounds and burns	11.9 (2015) 20.5 (2020)	+ 8.0	[Allied Market Research. 2016]
Medical adhesives and cements	6.9 (2015) 14.2 (2022)	+10.7	[Medcajet.2016]
Catheters	70.8 (2015)	+10.6	[Allied Market Research. 2016]
Materials for cell and tissue engineering	11.9 (2015) 45.5 (2022)	+21.0	[SmitheryApex. 2016]

determines the aspects of training of specialists who plan to work in this field. Currently, specific undergraduate and master degree programs are available in more than 250 universities around the world (mostly in the US). In Russia the master degree programs are available in D.Mendeleev University of Chemical Technology, St. Petersburg Polytechnic University, Siberian Federal University (Krasnoyarsk), Moscow State University of Design and Technology.

Several most important applications of biomaterials can be distinguished [5]:

– materials for implants and endoprostheses, including biodegradable endoprostheses used in cardiovascular surgery, bone surgery, ophthalmology, and dentistry, in soft tissue replacement and wound and burn treatment, in the production of resorbable suture material, etc;

– materials for systems with biological, especially medicinal, activity;

– materials for bioengineering (cell, tissue and genetic) technologies used as carriers and scaffolds for living tissue growth and delivery of genetic material into the cell;

– materials for the separation (usually sorption and membrane) systems that find their application in medicine and biology and used in hemodialysis and hemosorption devices, including those with electrosensitive coating;

– materials for biochemical analysis and synthesis used in microarrays and carriers for polypeptide and polynucleotide synthesis;

– materials for systems with enzymatic activity that contain immobilized enzymes, organelles and cells;

– materials for products that do not come into direct contact with blood and lymph, for example contact lenses and devices for external osteosynthesis;

– general purpose biodegradable materials, including those that can be degraded by microorganisms after use.

Polymeric implants [4–9]

Polymeric materials are a base for many groups of implants — objects implanted into the body by surgical methods where they "work" fully or partially surrounded by living tissues. The implants that replace removed internal organs or their fragments are commonly referred to as endoprostheses.

Depending on how well the implant material can decompose exposed to the surrounding environment, either a gradual decrease in the weight and volume of the objects implanted into body (biodegradation) is observed or, in case of indecomposable or slowly decomposable material, the thin tissue membrane (capsule) is formed around the implant, which is a protective reaction of the organism to a foreign object [10–17].

Currently, implants are widely used in surgery. The largest group of implants is the implants used in cardiovascular surgery, bone and soft tissues surgery, ophthalmology, and dentistry. Some implant groups comprise various products used in patients with skin defects, including wounds and burns, and those used as suture materials, etc.

Implants for the cardiovascular system [18–27]

For the manufacturing of cardiovascular implants that contact with blood (endoprostheses of vessels, cardiac valves, or the whole heart, circulatory support systems, such as endoprostheses of the left ventricle, pulsating balloons implanted into the aorta, coating of electric cardiac pacemaker leads), high hemocompatibility materials are used. These materials must not induce destruction and denaturation of the molecular and cellular components of blood, affect the salt and water balance and blood pH, or trigger formation of blood clots (thromboresistance).

Among the polymers with improved hemocompatibility, the "segmented" polyurethanes have found their practical application (such as block copolyurethanes with flexible blocks, e.g. polyether or polyester resins, polycarbonates, polysiloxanes, and blocks that ensure good intermolecular interaction), as well as polyethylene terephthalate, fluorine-containing carbon-chain polymers (expanded polytetrafluoroethylene, fluoron), polysiloxanes, and carbon-bearing composites.

But the search for materials with even better hemocompatibility is going on. The most promising here are hydrogel-coated surfaces, surfaces with immobilized thrombolytics and anticoagulants, and endoprosthesis surfaces with immobilized endothelial cells.

Examples of the prostheses used in cardiovascular surgery are shown in Fig. 1–3.

Implants for the skeletal system [1, 3, 6, 9, 28, 29]

Implants are also widely used in bone surgery for the replacement of damaged or removed parts of bones, elements of structures of artificial joints, fixators for fracture repair in osteosynthesis. For their manufacturing, polymers and composites with carbon and inorganic fillers, such as hydroxyapatite, are used.

Polymers used in bone implants must either possess high resistance to biodegradation (e. g., polymers used for joints endoprostheses), or decompose if the goal is to gradually replace the implant with living tissue (e. g., fixators for internal osteosynthesis, sealing compounds).

Among non-biodegradable polymers used to create bone implants, ultrahigh-molecular-weight polyethylene, polysulfones and polyformaldehyde are worth mentioning. Polyesters of hydroxycarboxylic acids, especially glycolic, lactic and hydroxybutyric, and their copolymers, are becoming increasingly important in the manufacturing of biodegradable implants that form non-hazardous metabolizable fragments when decomposing inside the body.

Polyacrylates (the so-called acrylic cement), poly-α-cyanoacrylates, and copolyurethanes serve as a polymeric base for adhesives and cements used for the attachment of endoprostheses of joints and bone fragments.

Fig. 4 and 5 show the examples of prostheses of hip and knee joints

Soft tissue implants [5, 7]

The best-studied implants for soft tissue replacement are breast endoprostheses - polysiloxane rubber bags with soft filler injected through the catheter before or after implantation. Despite the mass use of such implants, the filler issue has not been completely solved, as polysiloxane gels, oil emulsions and saline solutions used in some implants have certain drawbacks in terms of safety and mechanical characteristics.

For the filling of postoperative cavities in soft tissues, elastic materials, including expandable and hydrogel materials (polysiloxanes, polyurethane foams), are used. For the replacement of some internal membrane elements, for example, during the repair of the abdominal and thoracic walls, the use of polymeric mesh was suggested; once the mesh (polyolefin or expanded polytetrafluoroethylene) is placed inside the body, connective tissue starts to gradually grow through and around it.

The adhesives for soft tissue bonding during or after surgery are not widely used yet, although PEUR-, cyanoacrylate-, and protein-based adhesives developed for this purpose show good results in some cases. Among the known disadvantages of such systems are difficulty to provide a sufficient level of adhesion and hardening impeded by intense water supply to the bonded tissue, and low bonding strength.

Certain groups of biomaterials implanted into the soft tissues comprise soft polymeric implants, injectable polymeric systems for cosmetic purposes, and polymeric mesh.

Endoprostheses of ligaments and tendons [5, 7]

Endoprostheses of ligaments and tendons are of great importance in orthopedic surgery. Here, porous tapes of

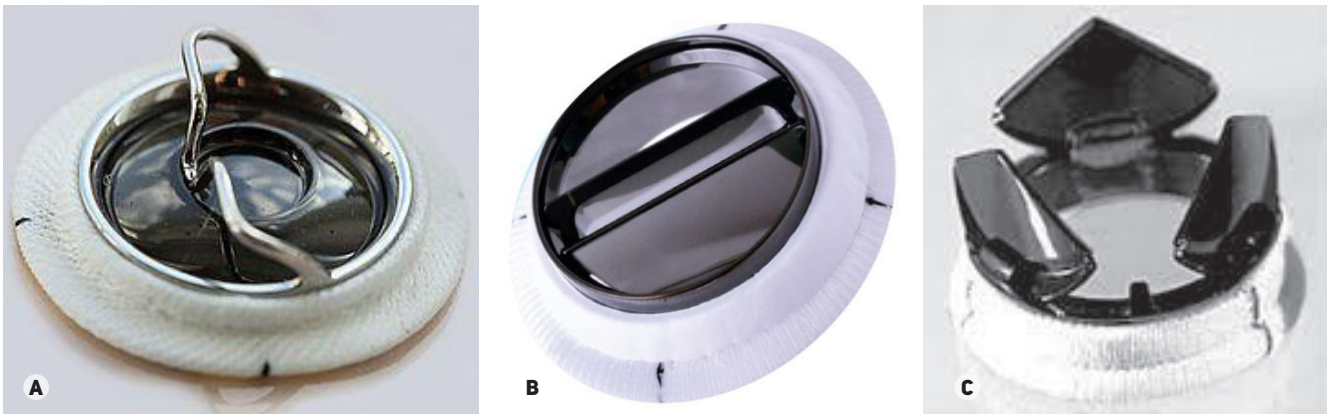

Fig. 1. Examples of structural heart valve endoprostheses: **(A)** disc endoprosthesis (Specialnoye konstruktorskoe buro medicinskoy tematiki, Russia); **(B)** bi-valved endoprosthesis (MedInzh, Russia); **(C)** three-valved endoprosthesis CorBit (Bakulev Scientific Center of Cardiovascular Surgery, Russia)

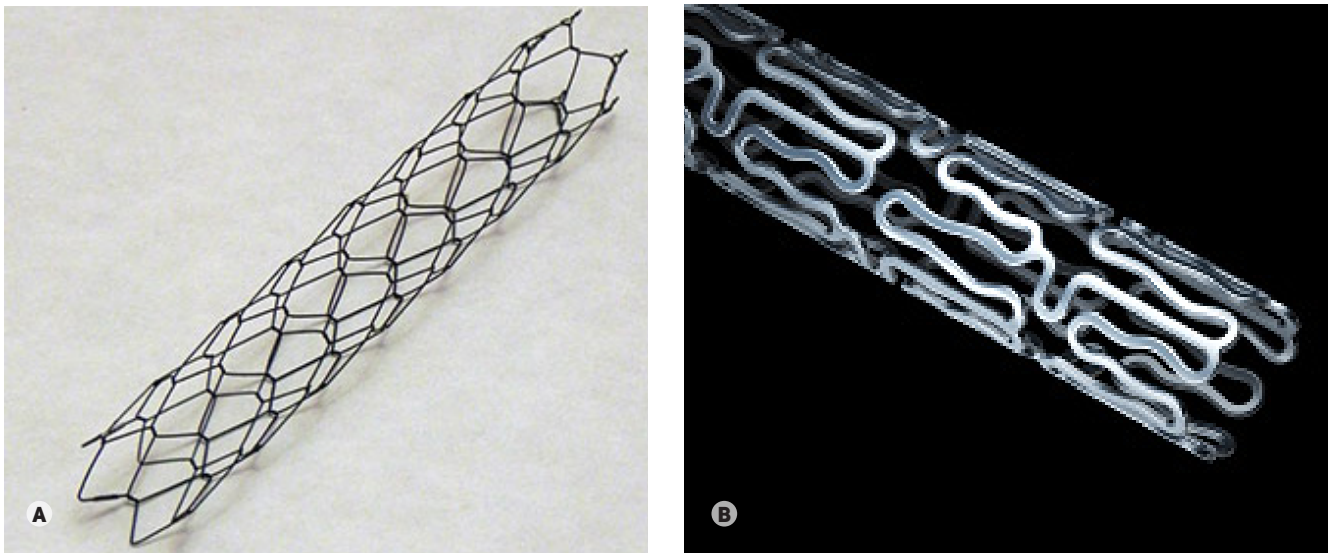

Fig. 2. Examples of vascular stents: **(A)** self-expanding wire stent Alex (Komed, Russia); **(B)** MULTI-LINK VISION Coronary Stent made with laser processing of a tube of an alloy of cobalt and chromium (Abbott Vascular, USA)

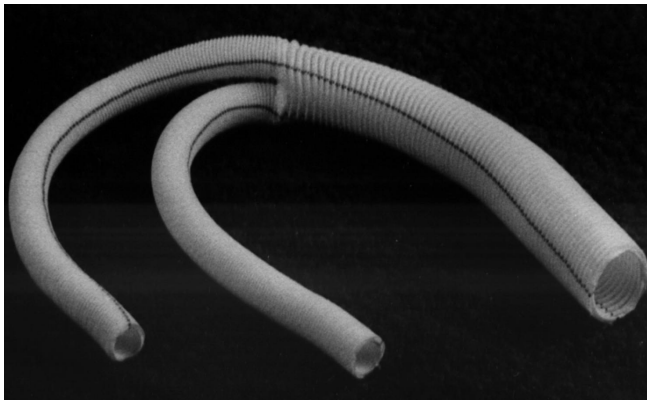

Fig. 3. Woven crimped bifurcation vessel endoprosthesis made of PET - fluorlone (PGTO Sever, Russia)

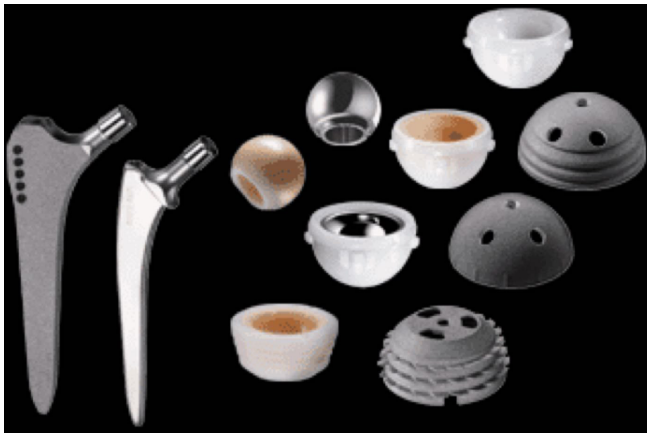

Fig. 4. Parts of the hip endoprosthesis by Endo Plus (UK)

Fig. 5. Parts of the Consensus knee prosthesis by Hayes Medical (USA)

polyethylene terephthalate and foamed polytetrafluoroethylene have found their application. The use of biodegradable polyesters of hydroxycarboxylic acids for the replacement of ligaments and tendons is actively studied. Such endoprostheses are designed to be replaced by living tissue.

It should be noted that muscle tissue endoprostheses have not been developed yet, although there are a number of studies on polymers that change their size depending on the electrical and physical characteristics of the environment.

Coatings for wounds and burns [5, 7]

Much effort has been made to create effective coatings for wounds and burns. The complexity of the problem is mainly determined by the fact that different stages of the healing process require materials with different combinations of characteristics (gas-permeable film and disperse sorbent, isolating and biologically active materials). However, the industry produces a significant range of such materials, including those containing several polymeric layers with different functions, in which various combinations of polymers, such as silicone block copolymers, polyesters of hydroxycarboxylic acids, PEUR, polyvinyl alcohol, alginates, collagen, chitosan, chondroitin sulfates, and some of others are used.

Polymeric implants in dentistry [5, 7]

Polymeric filling materials are a good example of how polymeric implants can be used in dentistry. Of particular interest are various hardening low molecular weight or oligomeric systems that contain unsaturated (meth)acrylate groups, epoxy compounds, and transition metal polycarboxylate complexes. At the same time, it should be noted that currently existing dental endoprostheses are made from metals and inorganic biomaterials.

Implants in ophthalmology [5, 7]

Polymeric implants have important role in ophthalmology. Thus, eye lens implants have found their application here, namely: monofocal and multifocal intraocular lenses made from polymethylmethacrylate and acrylate copolymers, and silicone materials; implantable contact lenses and intracorneal segments from polymethylmethacrylate, copolymers of collagen and acrylates; devices that reduce the intraocular pressure — shunts (silicone tubes) and valves manufactured from polyolefins, polymethylmethacrylate, and cross-linked silicones.

Suture materials [5, 7]

A separate group of widely used implants is comprised of suture materials, or rather, their filar component. The kits of suture filaments that usually contain functional polymeric coating in addition to the multifilament part are produced by many firms. Currently, sutures from both non-biodegradable polymers (polypropylene, polyamides, expanded polytetrafluoroethylene, polyethylene terephthalate, silk, cotton, flax) and biodegradable materials (catgut, polyesters of hydroxycarboxylic acids) are widely used. The polymeric coatings of suture filaments (polysiloxanes, copolymers of ethylene oxide and propylene oxide, copolymers of N-vinylpyrrolidone and acrylates) contain dyes, haemostatics and antimicrobial agents.

Polymers in the bioactive systems [30–40]

Polymeric biomaterials are used to create systems with different biological activity, i. e. the ability to affect biological objects, including the human body, by regulating their vital functions through stimulation, inhibition or development of certain features. The extreme manifestation of the biological activity is the biocidal action, when exposure to a substance (biocide) leads to the object's death.

Bioactive systems with polymeric components or fragments are designed for implementing various types of activity: they can

stimulate biological processes or inhibit them and have biocidal properties. Such systems can be divided into two groups; the first comprises forms with non-chemically incorporated bioactive substances (BAS), the second comprises polymeric bioactive substances.

Forms containing BAS that have no chemical bonds with polymers

Systems containing polymers in which bioactive substances have no chemical bonding with polymeric components are widely used in medicine. Such systems are insoluble in water, and the incorporated active substance enters body tissues owing to diffusion or system decomposition, including erosion. We can divide such products into two groups: those in which polymeric components do not affect the rate of BAS release and those in which polymeric components determine the rate of BAS release.

The examples of polymeric components that do not affect the rate of BAS release are powdered polymeric fillers of tablets, components facilitating their molding and ensuring they do not stick to molds. Here, starch, polyvinyl alcohol and other biologically neutral polymers are commonly used

The forms with non-chemically added BAS become increasingly important; here, the polymeric component determines the rate of BAS release to living tissues. Such insoluble systems, as well as polymers from which BAS is released due to the gradual degradation of its chemical bonding with a polymeric carrier (to be described later), are commonly referred to as systems with controlled release of the active substance. These systems can eliminate or reduce the impact of a narrow range of doses and concentrations required for producing a desired effect, which is beneficial for the patient, because excesses can lead to adverse reactions as the medication is not only delivered to the target organ, but also distributed throughout the body providing acute toxic, allergenic and carcinogenic effects. This complicates accurate dosing of the BAS. In addition, adverse reactions do not allow administering such amounts of BAS that can provide a long-term effect. With BAS susceptible to leaching, volatilization or biodegradation (which is often observed when using pesticides) and structural changes (typical for protein drug compounds), a positive effect is achieved through the use of excessive doses of the medication or its multiple administration, which considerably increases the costs.

The principle of controlled release is used in many forms of BAS. Thus, tableted forms of medications are widespread and well-known. They are most often used as preparations for enteral administration, but tableted forms for subcutaneous implantation are also known.

Polymeric tablet coatings delivering the drug to the desired area of the gastrointestinal tract have become widespread. For example, polymers used to create such coatings, marketed as Eudragit (Germany), contain ionogenic groups that determine the solubility of polymers in the environments with different pH. Thus, tablets coated with a polymer containing basic groups, for example copolymers of dimethylaminoethyl methacrylate with methyl or butyl methacrylates decompose in the acidic environment of the stomach. At the same time, tablets coated with polymers that contain acidic groups, for example copolymers of acrylic acid and ethyl methacrylate or metacrylic acid and methyl methacrylate, are stable in the stomach and decompose in the intestinal tract where pH ranges from 7.2 to 9.0.

Prolonged effect of the medication and reduced adverse reactions (unpleasant smell or bitter taste) make it possible to manufacture it as micro- and macrocapsules.

Widespread are various macromolecular systems in which the BAS is incorporated in the polymeric mass, from where it enters the body due to diffusion or after the gradual dissolution of the carrier. BAS-containing polymeric medicated films are used in ophthalmology for the prevention of coronary disease. They are storable and easily attach to the mucosal surface of the eye and gum (transmucosal preparations). For drug delivery, other polymeric systems are used, which work in a similar manner, for example coatings of suture materials or BAS-containing fibers themselves, catheters with antiseptics introduced into the polymeric mass, and others.

Transdermal systems (multilayer therapeutic systems glued to the skin) are one of the most promising forms of polymer-based drug substances used in adhesive patches and special devices. In general, the transdermal systems consist of an upper coating layer; a diffusion layer or a BAS- containing reservoir; a polymeric film that controls delivery of the active substance by diffusion; an adhesive layer that retains the system on the skin and ensures a direct contact with it; and a protective film of the adhesive layer removed before the system is glued to the skin. The diffusant is released from the BAS system, penetrates through the skin, reaches the subcutaneous blood vessels and spreads throughout the body.

Recently, a great deal of attention has been paid to nanosized carriers of medications, especially, liposomes, including modified amphiphilic polymers, nanospheres, dendrimers, and nanoaggregates. The optimal administration routes of colloidal systems that contain nanoparticles are injections (e.g., intravenous), inhalation, and oral administration. Nanoparticles are also used in eye drops.

Under development are BAS delivery systems that can function under specified conditions or in response to environmental conditions. Such systems are referred to “smart” or “intelligent” systems, or feedback-based systems. To some extent, they simulate the processes occurring in the body and can be physiologically optimal therapeutic systems if adjusted properly.

Another approach ensuring the delivery of a drug to the affected organ is based on introducing ferromagnetic substances to the drug followed by the exposure of the organ to the magnetic field.

It should be noted that the polymers with controlled release of BAS are used not only in medicine. Examples of such polymers are fertilizers encapsulated in a polymer shell that considerably reduces their consumption, fumigation devices and prolonged release forms of pheromones used in insect traps, and polymeric antifouling paints used to coat bottoms of ships.

Bioactive polymers

Of great importance are polymers whose bioactivity is determined by their macromolecular nature. In some cases they mimic natural polymers and can be used to replace natural components of blood. A good example here is macromolecular components of blood substitutes. Such polymers mimic two important functions of blood proteins: they maintain blood osmotic properties (components of antishock substitutes or blood substitutes with a hemodynamic effect) and ensure formation of complexes with toxic substances that enter the bloodstream (components of blood substitutes with

a detoxifying effect). Oxygen carriers and their polymeric forms (modified hemoglobin) are also used as blood substitutes.

Blood substitute components are used as water-soluble non-ionogenic polymers. Polymers used to obtain components of blood substitutes with a hemodynamic effect must have a sufficiently high molecular weight (at least 50-60 kDa). Here, polymers of natural origin can be used as a base after certain chemical modification that can decompose inside the body and then be excreted from it. They include dextran, partially hydroxyethylized starch and denatured protein gelatin derived from collagen.

The polymeric components of blood substitutes with detoxifying properties are polymers with a molecular weight of about 10 kDa. They are easily excreted in the urine, so in these products the carbon-chain polymers are used, such as poly-N-vinylpyrrolidone (Hemodez and Neohemodez by Biohimik, Russia), poly-N-(2-hydroxypropyl)methacrylamide (Duxon, Czech Republic), and polyvinyl alcohol (Polidez by Himitek, Russia). These polymers exhibit strong toxicant-complexing properties.

It should be noted that the production volume of the polymeric components of blood substitutes with hemodynamic and detoxifying effects exceeds the production volume of other medical polymers.

Water soluble polyelectrolytes, polymers with cationic, anionic, and N-oxide groups also exhibit biological activity, such as microbicidal, adjuvant, coagulant, or anticoagulant; among them is polyoxidonium (copolymer of N-oxide 1,4-ethylene piperazine and (N-carboxyethyl)-1,4-ethylene piperazine bromide) that has immunomodulating properties and can be used as an adjuvant for synthetic vaccines.

We should also mention a few high-molecular compounds in which BAS or a group determining the activity of the substance are linked with the polymer by a chemical bond that does not break as the system is being used. Among such compounds are stabilized (immobilized) enzymes, including those used for the formulation of water-soluble drugs. Bound to a polymeric carrier or a modifier, the enzyme becomes more resistant to denaturation; for insoluble forms, such binding allows the enzyme to participate in the enzymatic process multiple times. The best studied are products based on dextran-modified enzyme streptokinase (Omela, Russia) used as an effective fibrinolytic agent.

Another example of systems with permanent bonding (immobilization) is a group of immunoactive polymers that are conjugates of a polymeric carrier and active, usually low molecular weight group (hapten) that stimulates receptors of immune cells. The research in this area led to the development of a series of vaccines - conjugates of polyoxidonium with a number of antigens, such as hemagglutinin and neuraminidase of three influenza viruses: A (H1N1 and H3N2) and B (Grippol by NPO Petrovax Farm, Russia), timothy grass pollen allergoid (Timpol), birch pollen allergoid (Berpol), and wormseed pollen allergoid (Polpol).

Bioactive polymers

Significant disadvantages of low molecular weight drugs, bio-regulators and biocides are their nonoptimal doses and concentrations, limited action period, rapid incidental consumption, and insufficient solubility, all of which can be eliminated or considerably reduced by using BAS in the form of a chemical compound hydrolysable over time, with polymer-based carriers or modifiers. Such chemical compound is actually a new bioactive polymer whose chemical structure differs from that of the original polymeric carrier. The chemical bond between the BAS and the polymeric carrier may degrade at a certain rate, usually by hydrolysis, sometimes involving enzyme systems. The rate of this gradual (prolonged) release can be controlled by the polymeric structure or the structure of a biologically active system. Therefore, such systems, as well as previously discussed forms with regulated BAS release, can be called systems with controlled BAS release (controlled release systems).

In contrast to insoluble drug formulations, polymeric BAS derivatives can be produced in the water-soluble form, which determines broad possibilities for their use. In these systems, controlled release of an active substance provides for the long action of the medication without overdosing and therefore side effects. Production of polymers that ensure target delivery of the medication to the affected organ is a major area of development of new systems with controlled release of an active substance.

Derivatives of poly-N-vinylpyrrolidone, poly(N-2-hydroxypropyl) methacrylamide, polyvinyl alcohol and dextran are often used as polymeric carriers for the described group of systems.

It should be noted that in addition to polymers with therapeutic properties, there are systems that exhibit bioregulatory or biocidal activity against other groups of organisms; for example, they regulate plant growth or have fungicidal properties [41-43].

Polymers in bioengineering [44, 45]

The processes and methods falling within the concept of “bioengineering” are principally aimed at optimizing the vital function of cellular systems in order to obtain practically valuable producers and tissues that can be used for the replacement of tissues and organs. Practical implementation of bioengineering methods relies to a large extent on the use of various polymeric carriers and substrates. Although the methods related to bioengineering are subdivided into cell, genetic and tissue engineering, in actual practice they often complement each other.

Cell engineering represents a field of biotechnology and is based on the cultivation of cells and tissues capable of producing the required substances in vitro (outside the body). Cell culture is often performed using porous microcarriers, such as derivatives of DEAE-dextran or sephadex (cross-linked dextran). Interior cultivation of cells can be implemented if cells are encapsulated in semipermeable polymeric microcapsules whose shell (cross-linked polylysine, agarose) allows nutrients to get through.

Tissue engineering aimed at cell culture for the regeneraion of damaged or lost tissues is one of the most promising areas of medicine and is based on the formation of the desired tissue structure from the cells seeded on a specific substrate (stem cells in particular).

As a discipline, tissue engineering was based on projects aimed at creating “artificial” tissues and organs and research on transplanting cells and biologically active components to the carriers to repair lesions in various tissues of the body. The basic principle of this approach is the development of biodegradable carriers combined with donor cells and/or bioactive substances and their implantation into the damaged organ or tissue. To grow the tissue in the body, the cultured cells must stay on the carrier for some time: when its biodegradation is too rapid, the cells can be washed from it with the body

fluids. On the other hand, if the substrate "lives" for too long, it interferes with the normal process of tissue or organ regeneration. Among the polymers satisfying the described requirement are polyglycolide, polylactide, copolymers of glycolic and lactic acids, polycaprolactone, polypropylene fumarate, polyanhydrides, and polyorthoesters.

Genetic engineering makes use of the achievements of such sciences as molecular biology, cytology and genetics and is similar to targeted drug delivery in terms of nature of scientific approaches and techniques, since its ultimate goal is the delivery of nucleic acids or their fragments into the cell. The most appropriate technique for delivering the genetic material into the cell is endocytosis of its complexes with polymeric carriers, usually polycations (polyethyleneimine, polylysine and others). This method (transfection) has significant advantages over other methods of genetic material delivery, such as sonoporation, electroporation, microinjection, or the use of viral carriers. The most advanced biological objects in which genetic engineering techniques can be applied are microorganisms and plant cells, although there have been a number of works recently in which genetically engineered animals were used. For humans, genetic engineering can be an effective remedy for genetic disorders and predisposition to certain diseases.

Polymers in biocatalytic processes [46–49]

Development of artificial biocatalysts based on modified enzymes is of great importance for medical bioengineering or systems for bioanalysis, as noted in this review in the relevant sections. Besides, these biocatalysts play a very important role in industrial biotechnology. This is due to the significant disadvantages of enzymes extracted from living tissues, in particular the instability of their globular structure in response to various influences (susceptibility to denaturation). This applies to both simple and complex enzymes that have a non-protein component (coenzyme) in their structure, in addition to protein components. Another significant technological disadvantage of enzymes is their solubility in water, which participates in most enzymatic industrial cycles and hinders enzyme separation after the process is completed and its further re-use.

Those disadvantages were to a large extent neutralized by binding the protein macromolecule of the enzyme to the insoluble carrier that can be quite easily separated from the reaction mixture and re-used in stirred-tank reactors or column reactors in continuous processes. Furthermore, the binding of the enzyme macromolecule to the carrier increases its conformational stability and stabilizes it in the presence of denaturing factors.

The carriers used to obtain immobilized enzymes come in various forms, such as granules, fibers, membranes intended for filling columns, helices, rings, tissues, etc. Although for the manufacturing of such carriers, especially granular, inorganic materials are also used, most of the industrial carriers for immobilized enzymes are made from polymers or their composites with inorganic materials.

To date, a significant number of methods of binding of enzyme macromolecules to a carrier have been developed. They are based either on enzyme adsorption on the carrier surface, chemical binding of a protein globule to the functional groups of the carrier, or its inclusion into the polymeric mass of the carrier. Protein inclusion in polymeric mass is used for the formation of fibers and films (membranes) that must exhibit enzymatic activity.

The cells themselves can be used as biocatalytic systems if they are immobilized, primarily by microencapsulation or inclusion into hydrogel granules (derived from agarose or polyvinyl alcohol, etc).

Polymers in the separation processes [5]

The processes of sorption and membrane separation, used in a variety of technologies, have found wide application in medicine and biology. In addition to the isolation and purification of products of various biotechnological reactions, they are used for the purification and detoxification of biological fluids, such as blood and lymph.

Polymeric biomaterials used in these processes come in direct contact with blood or lymph and must be highly hemocompatible Just as polymeric implants that "work" in the blood stream, they must not cause blood clots, injure formed elements, cause denaturation of the protein components and release toxic compounds.

The membrane method of blood purification (hemodialysis and hemofiltration) performed in hemodialyzers consists in removing harmful substances and toxins from the blood, when the dialyzable liquid (blood) flows by one side of the polymeric membrane and the dialysis fluid flows by the other side. When using ultrafiltration membranes, low- and medium molecular weight substances pass through them under the influence of a concentration gradient, but high-molecular weight components of blood do not pass through. If the dialysis fluid pumped in counterflow to the dialyzable liquid is replaced with fresh fluid quite frequently, harmful substances can be removed from the dialyzable liquid.

Polymeric ultrafiltration membranes are also used for blood oxygenation carried out in the oxygenation unit cells of the "artificial heart-lung" machine. Here, blood flows by one side of the membrane, and a gaseous medium enriched with oxygen flows by the other side. Thus, due to the difference in the partial pressure, oxygen enters the blood stream. Carbon dioxide passes through the membrane in the reverse direction. This device is indispensable in surgeries performed on the cardiovascular system.

Membrane separation is also used for the decontamination of drug solutions, when methods of stronger impact on the disinfectant, such as heat or radiation sterilization, are not applicable.

Sorption is used to purify various biological fluids: blood (hemosorption), blood plasma (plasmasorption), lymph (lymphosorption), lymph plasma (plasma-lymphosorption). The sorbents used in such processes are granular or powdered systems that are usually subdivided into nonselective, capable of absorbing several substances, and selective used for extracting specific sorbates.

Selective sorbents are polymeric systems containing functional groups that ensure ion exchange or biospecific binding to the extractable substance, including immune sorption.

A separate type of sorption decontamination processes is enterosorption related to the use of sorbents that extract toxins from the gastrointestinal tract. For this purpose, the sorbents based on activated carbons are used, as well as polymeric sorbents based on lignin, cellulos and crosslinked polyvinylpyrrolidone.

Polymers in bioanalytical systems and synthesis of biopolymeric analogues [5]

The use of polymers in various bioanalytical devices and medications is extremely important for the development of

medical and biological sciences and technologies. It should be noted that application of polymers in biomedicine is determined not only by the specific branch of this science, but also by the fact that polymer-based devices for bioanalysis come in direct contact with living tissues, such as biological fluids and cell suspensions.

Among the research methods used in biochemistry, biology and medicine are bioanalytical methods, such as electrophoresis and immunoelectrophoresis (on plates, discs, in columns and capillaries), that make use of polymeric carriers, such as agarose and polyacrylamide gels and their modifications; various chromatographic methods based on the use of polymeric sorbents, including affinity- and immunosorbents; enzyme immunoassay that makes use of polymeric substrates; latex agglutination test systems based on the "curdling" of polymer latexes derived from polymeric microspheres whose surface is modified by a component of the antigen-antibody pair.

Polymers are an important component of various biosensors, such as membrane-electrode devices containing immobilized enzymes. Moreover, special attention has been paid recently to the fast bioassay methods based on the use of biosensors.

Polymeric carriers are a crucial component of polypeptide and polynucleotide synthesis. Only after the discovery of solid-phase methods for their preparation, it became possible to solve extremely difficult or impossible tasks, such as separation of the products of the addition reaction from the initial products and reagents given their solubility in water, and preservation of macromolecular chains in the course of optical isomer synthesis. Also, solid-phase synthesis techniques for the preparation of polysaccharides have been developed. The evolution of this approach described in many publications enabled to obtain a large number of synthetic polypeptides and polynucleotides, and in many cases their synthesis was automated.

Solid-phase amino acid sequencing of natural macromolecules based on the use of polymeric carriers is no less important; here, the stepwise cleavage of the terminal fragments, combined with the amino acid analysis of the biopolymer, reveals the sequence of the respective links in the macromolecule.

Biodegradable polymers of general purpose [5, 11]

In recent years, much attention has been paid to the development of biodegradable materials of general purpose. It is predicted that such environment-friendly materials will be widely used not only in medicine, but in the manufacturing of degradable packaging, disposable items, special types of clothing, etc. Several groups of such materials are worth mentioning.

Natural polymers, especially polysaccharides and proteins, and their modifications are still used as before. Cellophane remains a very popular packaging material. Composites based on acetate cellulose and starch hold some promise too.

Composites based on polyolefins and starch are promising film materials with a large tonnage capacity and a high biodegradation rate. Products based on these composites can be quickly fragmented and absorbed by soil microorganisms.

An important group of biodegradable polymers comprises polymers of hydroxycarboxylic acids, primarily polylactic acid (polylactide), large-tonnage production of which has been launched in some countries in recent years.

Non-implantable medical polymeric devices and products [5]

Among these products, contact lenses should be noted in the first place; they are manufactured in large quantities in the developed countries. Despite the fact that they are placed on the cornea, they are washed with the tear fluid and therefore must have high biocompatibility. Strictly speaking, contact lenses are not implants because they do not come in direct contact with the body liquids, such as blood and lymph. The most common materials for contact lenses are cross-linked silicone systems with good optical characteristics and high gas and vapor permeability, copolymers of 2-hydroxymethylmethacrylate and ethylenebismethacrylate, and in some cases crosslinked copolymers of acrylamide.

Polymers play an important role in the medical industry as raw materials for the manufacturing of orthopedic and dental equipment. This area of polymer application is of special interest and is not the subject of this review

CONCLUSION

As seen from this brief review, the materials and products based on the different types of high-molecular compounds are very widely used in medicine and biology. There are some specific aspects of their application that distinguish this field from other areas of chemistry and technology of high-molecular compounds. Firstly, most polymers for biomedical application are produced in small quantities or come as specially prepared and carefully purified batches of conventional polymers. In some cases, the annual demand for these polymers does not exceed a few kilograms or tens of kilograms. Secondly, many of these polymers are manufactured using small-size equipment, often made of glass, according to the principle of flexible manufacturing systems. Thirdly, since many of these products come in direct contact with a living organism, their manufacturing must meet GMP requirements. Finally, during the development of such products one should consider that they must be approved by the government agencies. These factors have a strong impact on training programs for researchers and technicians who plan to work with polymers employed in medicine and biology.

Another important aspect of this area of knowledge is related to the constant updating and improvement of the methods of application of polymeric materials and products, which necessitates a serious effort aimed to improve the structures and properties of the polymers and to develop new high-molecular compounds that meet the specified requirements.

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THE USE OF IMPLANTS FOR SURGICAL TREATMENT OF CONGENITAL DIAPHRAGMATIC HERNIA IN NEWBORNS

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Congenital diaphragmatic hernia (CDH) is an absolute indication for surgical treatment. In case of extensive defects of the diaphragm, such as diaphragmatic aplasia, the use of implants is required. So far, there is no unanimous opinion on the type of the implant. The article presents a comparative analysis of treatment of 40 newborns with left pseuso-CDH. All patients received thoracoscopic repair of the diaphragmatic cupula. The patients were divided into two groups according to the type of the implant: 16 newborns received Ecoflon synthetic implants (Ecoflon Scientific and Production Complex, Russia) and 24 newborns received Permacol biologic implants (Tissue Science Laboratories, UK). The study demonstrated the advantage of the biologic implant over the synthetic one: the surgery took less time (106 minutes compared to 144 minutes with Ecoflon, $p < 0.05$); relapses were also more rare (28 % and 54 %, respectively; however, p was >0.05); no implant rejection was observed (with Ecoflon, two patients responded with inflammation, $p < 0.05$).

Keywords: newborns, congenital diaphragmatic hernia, thoracoscopy, implant, implant materials, Ecoflon, Permacol

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ПРИМЕНЕНИЕ ИМПЛАНТОВ В КОРРЕКЦИИ ДИАФРАГМАЛЬНОЙ ГРЫЖИ У НОВОРОЖДЕННЫХ

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Врожденная диафрагмальная грыжа (ВДГ) — патология, которая требует обязательной хирургической коррекции. При значительных дефектах диафрагмы, например аплазии ее купола, зачастую возникает необходимость в использовании имплантационных материалов. До сих пор нет единой точки зрения по вопросу выбора импланта. В статье представлены результаты сравнительного анализа лечения новорожденных (n = 40) с левосторонней ложной ВДГ. Всем пациентам была выполнена торакоскопическая пластика купола дифрагмы. По типу использованного имплантационного материала детей разделили на две группы: для первой (n = 16) применяли синтетические импланты «Экофлон» («НПК "Экофлон"», Россия), для второй (n = 24) — биологические импланты Permacol (Tissue Science Laboratories, Великобритания). Результаты исследования показали преимущества биологического импланта: время операции при его использовании было меньше (106 мин против 144 мин при использовании «Экофлона», $p < 0,05$); число рецидивов — также меньше (28 % против 54 %, однако $p > 0,05$); случаев отторжения импланта не было (при использовании «Экофлона» у двух пациентов началось воспаление, $p < 0,05$).

Ключевые слова: новорожденные, врожденная диафрагмальная грыжа, торакоскопия, имплант, имплантационный материал, «Экофлон», Permacol

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Congenital diaphragmatic hernia (CDH) is a potentially fatal malformation that leads to death without surgical treatment. For effective diagnostics and management of various pathologies in newborns with low weight and narrow chest, advanced video equipment and tools for mini-invasive surgery have been introduced. However, many issues of CDH treatment are still a matter of discussion, such as criteria for selecting a particular surgical technique, indications for endoscopic surgery and a surgery type, especially in the case of extensive defects of the diaphragm, and the choice of patch type if a patient does not

have sufficient tissue for grafting. The vast clinical experience of the medical institution is often the key to an adequate solution.

Surgical treatment of CDH is aimed to close the diaphragmatic defect by bringing its edges together and fixing them with interrupted sutures. Difficulties may arise if the defect is large (e.g. diaphragmatic aplasia) and the edges cannot be brought together even after the posterior leaf has been mobilized. In this case, patch repair is indicated [1–8]. The research [9] showed that in infants with diaphragm aplasia the postoperative survival rate was 57 %, compared to the survival rate of 95 % in patients with smaller defects.

We have analyzed a number of studies [3, 4, 6, 8] on primary repair of the diaphragm in infants with diaphragmatic aplasia and discovered that the most frequently used types of patches were synthetic non-absorbable patches; biological and composite non-absorbable materials were the second most frequent type. Generally, the highest relapse rate was seen in patients with biological implants (approximately 30 % of cases), however, with the other two types of materials it was almost the same (approximately 26 %). More significant differences were seen between the implants produced by different manufacturers [5, 9, 13].

The aim of our research was to compare the efficacy of the synthetic implant Ecoflon (Ecoflon Scientific and Production Complex, Russia) and the biological implant Permacol (Tissue Science Laboratories, UK) in the surgical treatment of congenital diaphragmatic hernia in newborns.

METHODS

The study included 40 neonates with left pseudo-CDH treated in N. F. Filatov Pediatric City Hospital No. 13, Moscow, Russia, from 2008 to 2015. All children received thoracoscopic repair of the diaphragmatic cupula with implants. Depending on the type of material, the neonates were divided into two groups: group 1 included 16 children who received the Ecoflon implant, and group 2 included 24 children who received the Permacol implant. All children were born full-term, with an average body weight of more than 3 kg. Further details are given in table 1. No statistically significant intergroup differences were revealed. Comorbidities were mainly congenital heart defects and genetic syndromes (Edwards syndrome in three cases and Patau syndrome in one case); extrapulmonary sequestration was observed in one patient from group 2.

All children received thoracoscopic repair of the diaphragmatic cupula with implants. The surgery was performed after stabilization of the general condition of the neonates.

The patient was placed in the right lateral decubitus postition on the operating table. The surgeon and the assistant stood at the patient's head, the monitor was located opposite. The reconstruction of the diaphragm was performed using three trocars (3 and 4 mm in diameter). CO_2 pressure in the pleural space was maintained at 3–7 mmHg, CO_2 flow rate was 1–2 l/min. The trocars were placed through the following portals: the endoscopic portal in the third intercostal space along the midaxillary line; the instrumentation portals in the third or fourth intercostal space along the posterior axillary line and in the third intercostal space along the anterior axillary line. After the examination of the pleural cavity, the abdominal organs were successively brought down into the abdominal cavity. The edges of the diaphragm were mobilized on the perimeter of the defect, thorough mobilization of the rear lip off the upper pole of the left kidney and the retroperitoneal space was conducted. After the retained muscular tissue of the diaphragm was brought together, interrupted suturing without tension was applied. A patch was formed from the implantation material corresponding to the size of the defect. Finally, drainage of the pleural space was performed. All children had postoperative prolonged mechanical ventilation (MV) until their cardio-respiratory function was normalized and spontaneous breathing was recovered.

The implant materials had to meet a number of specific requirements: they should be durable and flexible, have good modeling properties, be resistant to the liquid environments of the body and infections, non-responsive, hypoallergenic, and non-cancerogenic.

The synthetic material Ecoflon (Fig. 1) was first used in 2008 for thoracoscopic repair of extensive defects of the diaphragm. It is polytetrafluoroethylene-based and has a special nodular fibrillar structure with considerable porosity (up to 90 %). Ecoflon implants are flexible, elastic, and resistant to bending, twisting and external squeezing in unfavorable anatomical conditions. There are two functionally different surfaces: a microporous surface that prevents the formation of adhesions, and a macroporous surface that initiates the growth and development of fibroblasts. The disadvantages of the material include its relative susceptibility to infection, which is associated with multifilament and microporous components that cover bacterial agents. The Ecoflon implant is 1 mm thick. After an Ecoflon patch was formed, it was introduced through the wound and fixed along the perimeter of the defect with interrupted sutures with the microporous side facing the abdominal cavity. The surgical knots were tied extracorporeally.

The biological material Permacol (Fig. 2) has been successfully used since 2012. This implant is made of pig skin and is basically a pure cross-linked collagen and elastin free of cellular structures and fatty tissue. This material does not have any antigenic properties and induces minimal inflammatory response that is no different from the normal reparative process. The collagen fibers form the framework for the reparative tissues and vascularization. Due to its cross-linked structure, it is resistant to tissue and bacterial enzymes,

Table 1. Comparative characteristics of newborns with congenital diaphragmatic hernia

Index	Group 1 (n = 16)	Group 2 (n = 24)	P-value
Sex, m/f	10/6	10/14	–
Gestational age, weeks (min; max)	38.1 ± 2.4 (33.0; 41.0)	38.8 ± 0.8 (37.0; 41.0)	p >0.05
Birth weight, g	2880.0 ± 645.0 (1950.0; 4300.0)	3378.1 ± 473.0 (2580.0; 4600.0)	p >0.05
Age at the time of surgery, days	2.7 ± 1.8 (1.0; 7.0)	4.0 ± 1.4 (1.0; 9.0)	p >0.05
Comorbidities	3 (19 %)	6 (25 %)	p >0.05
Antenatal diagnosis	13 (81 %)	20 (83 %)	p >0.05

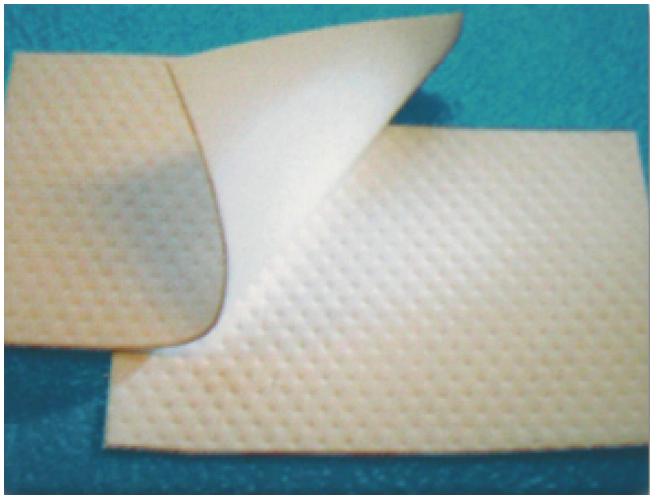

Fig. 1. Synthetic implant material Ecoflon (Ecoflon Scientific and Production Complex, Russia)

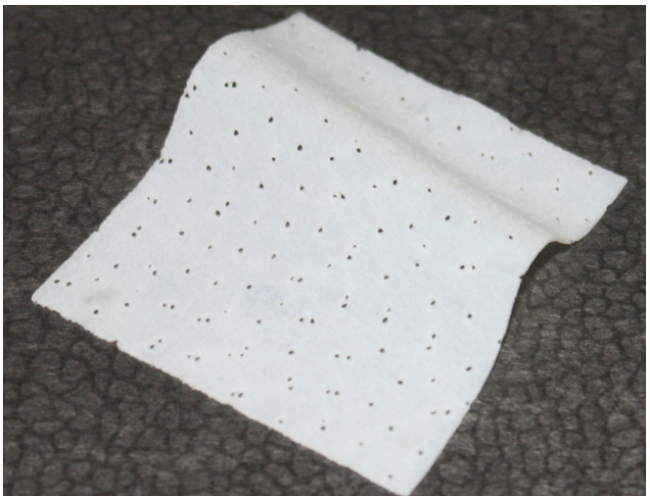

Fig. 2. Biological implant material Permacol (Tissue Science Laboratories, UK)

therefore, it is non-resorbable, non-deformable, and ensures the continuous strengthening of soft tissues without causing adhesions. Permacol does not stimulate suppuration and can be used in patients with controlled infections or at high risk of surgical site infections. The material thickness is 0.5 mm. The implant was introduced through the right trocar portal. Then its edges were sutured to the retained muscular rims, the anterior, medial and posterior regions of the diaphragmatic cupula with interrupted sutures. In the absence of a muscular layer, the lateral part of the defect was sutured to the chest wall with full-thickness sutures.

The following parameters were analyzed: surgery duration, location of the liver in the pleural space, MV duration and the number of cases when high-frequency MV (HF MV) was used, hydrothorax duration and the number of chylothoraces, the onset of enteral feeding and the number of cases of gastroesophageal reflux (GER), the frequency of relapses and implant rejection, and also the number of deaths.

Patients with chylothorax received the antisecretory drug Sandostatin (Novartis Pharma, Switzerland) intravenously. The starting dose was 80 mg/kg a day; the maximum dose was 120 mg/kg a day. Treatment duration was determined individually for each patient.

In patients with GER laparoscopic Nissen fundoplication was performed.

Recurrent congenital diaphragmatic hernia is clinically manifested through progressing respiratory distress and dysphagia. However, in order to detect asymptomatic relapses, control chest X-rays were performed in all patients 1, 3, 6 and 12 months after surgery. In doubtful cases, multislice helical computed tomography of the abdominal and thoracic cavities was performed. Once the diagnosis was confirmed, revision surgery was performed.

The C-reactive protein and white blood cell count were used as inflammation markers.

Parents gave written informed consent.

RESULTS

The surgical treatment results are presented in table 2.

Fixation of synthetic implants took longer than preparation of a biologic patch: mean time was 144 and 106 min, respectively ($p < 0.05$). The presence of the left lobe of the liver in the left hemithorax indicates the severity of the diaphragmatic defect corresponding to subtotal or total aplasia. Severe defects were more frequent in group 2 than in group 1, but differences were not statistically significant.

The mean duration of MV in both groups was almost the same. However, patients in group 2 required HF MV more often compared to group 1, which indicated a more severe cardio-respiratory dysfunction. However, the intergroup difference in this parameter was not statistically significant — perhaps, due to a moderate sample size.

One of the postoperative complications is chylothorax. In patients with congenital diaphragmatic hernia, chylothorax is thought to be the result of increased superior vena cava pressure in the presence of concomitant pulmonary hypertension. Another hypothesis is that chylothorax is a response to inflammation. In any case, chylothorax is preceded by hydrothorax, whose duration depends on the degree of pulmonary hypoplasia. The average duration of hydrothorax and the number of chylothoraces were similar in both groups. However, only one patient from Group 1 required Sandostatin therapy for over 3 weeks, while in group 2 there were 3 such patients.

An important indicator of a normal postoperative period was the start of enteral feeding and baby's ability to consume the amount of food normal for his/her age. As shown in table 2, enteral feeding started much earlier for the patients in group 2 compared to the patients in group 1: in average, on day 6 and 12, respectively ($p < 0.05$). One of the possible causes here was the absence of inflammation revealed by the blood test.

Gastroesophageal reflux is caused by the dilation of the esophageal hiatus after the reconstruction of the diaphragmatic cupula. This complication was seen in both groups with almost equal frequency: 4 and 5 cases in group 1 and group 2, respectively ($p < 0.05$). Our study showed that GER occurring after diaphragm repair is resistant to standard treatment and requires surgical correction.

Relapses were observed in 6 cases (54 %) in group 1 and in 5 cases (29 %) in group 2, but the difference was not statistically significant. In group 1 an infectious complication was detected in 2 patients: patch rejection was observed 2 and 3 months after surgery. The rejection manifested clinically as granuloma formation on the lateral surface of the chest in the site of the full-thickness suturing. Removal of granulomas and ligatures was performed for both patients, but the inflammatory process persisted, which determined the necessity of surgical intervention. Through the incision on the chest it was revealed that the bottom of the fistula channel was the implant.

Table 2. Results of thoracoscopic repair of congenital diaphragmatic hernia in newborns using Ecoflon and Permacol implants

Index	Group 1 (n = 16)	Group 2 (n = 24)	P-value
Intraoperative characteristics			
Duration of surgery, min (min; max)	**144 ± 28 (100; 180)**	**106 ± 10 (95; 126)**	p <0.05
Location of the liver in the pleural cavity	4 (25 %)	8 (33 %)	p >0.05
Characteristics of respiratory intensive care			
Duration of MV, days (min; max)	15.4 ± 8.8 (4.0; 46.0)	16.0 ± 7.4 (6.0; 42.0)	p >0.05
Number of cases of HF MV	2 (12 %)	8 (33 %)	p >0.05
Characteristics of hydro- and chylothorax			
Duration of hydrothorax, days (min; max)	14.6 ± 2.8 (4.0; 27.0)	14.7 ± 2.8 (4.0; 37.0)	p >0.05
Number of cases of chylothorax	4 (25 %)	5 (21 %)	p >0.05
Characteristics of enteral status			
Onset of enteral feeding, days after surgery (min; max)	**12.9 ± 2.0 (2.0; 15.0)**	**5.1 ± 2 (2.0; 11.0)**	p <0.05
Number of cases of gastroesophageal reflux	4 (25 %)	5 (21 %)	p >0.05
Characteristics of implant condition			
Number of relapses	6 (54 %)	5 (29 %)	p >0.05
Number of cases of implant rejection	2 (12 %)	0	p <0.05
Survival rate			
Number of deaths	5 (31 %)	7 (29 %)	p >0.05

The latter was freely removed from the chest cavity. No changes in the implant material were identified macroscopically.

Death occurred in 13 cases: 5 (31 %) patients in group 1 and 7 (29 %) patients in group 2 (p >0.05). The lack of statistically significant differences demonstrates that postoperative lethality was not caused by the diaphragmatic defect, but resulted from severe cardio-respiratory dysfunctions and intractable pulmonary hypertension, i. e. was a consequence of pulmonary hypoplasia and the severe cardio-respiratory pathology resistant to any therapy.

DISCUSSION

The Permacol implant allows for shorter surgery time since it can be introduced into the thorax through the trocar channel without removing the trocar. Given that Ecoflon is thicker and has less compressibility, one of the operation trocars must be removed to extend the incision at the site of the trocar placement; next, the implant must be placed into the pleural cavity and after that the trocar can be re-introduced. Another factor influencing the duration of the surgery is the process of the implant fixation. Specifically, Ecoflon must be positioned with the macroporous surface facing the chest and the microporous surface facing the abdominal cavity, while both Permacol surfaces are identical and their position is irrelevant for fixation. Another technical difficulty in fixing Ecoflon is its ability to absorb light making it hard to determine how accurate the implant is fixed to the edges of the diaphragmatic defect.

Nowadays, various types of implant materials are used for correction of major defects of the diaphragm [11, 13, 14]. However, the survival rate of newborns with this pathology is low, so it is very difficult to compare the results of treatment by the type of the implant. Nevertheless, scientific research in this field yields important results. Thus, the guide of Molloy [11] presents the scientific analysis of the use of implant materials of various types and the experimental data. Also, the advantages of biologic implants have been shown: they ensure better tissue regeneration than synthetic implants and do not cause inflammation. Some publications report recurrent congenital diaphragmatic hernia when prostheses are used for its repair. Riehle et al. [8] conducted a number of studies using the Gore-Tex/Marlex implant and observed a relapse in only one of 28 patients, i. e. in 3.6 % cases. At the same time, Mitchell et al. [10] conducted a comparative analysis of efficacy of repair with Gore-Tex and Permacol implants and reported relapses in 8 of 29 patients (28 %) who had received the implanted Gore-Tex, and zero relapses in all 8 patients with the implanted Permacol. Grethel et al. [4] also conducted a comparative analysis of efficacy of repair with synthetic and biologic implants. Their study showed that after Gore-Tex implantation, relapses occurred in 17 of 57 patients, while after Surgisis (a bioactive material) repair, relapses occurred in 12 of 27 patients.

Thus, currently there is no consensus on the use of implant materials. However, most authors believe that the use of biological materials is more promising because the latter are better integrated into the patient's own tissues and do not cause inflammatory response, which depends not only on the properties of the material, but also on the specific aspects of conservative therapy in the postoperative period.

CONCLUSIONS

Our study has found no statistically significant differences between the synthetic implant material Ecoflon and the biological implant material Permacol with regard to the survival rate, the number of relapses and the occurrence of gastro-esophageal reflux. However, Permacol is more beneficial for patients with extensive defects of the diaphragmatic cupula: it allows for shorter surgery time and earlier enteral feeding and causes no inflammatory response.

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THE USE OF SYNTHETIC SLINGS IN SURGICAL TREATMENT OF EPISPADIAS IN BOYS

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The treatment of urinary incontinence in epispadias, which is malformation of the lower urinary tract, is a pressing problem due to the severity of congenital anatomic and functional pathology and the lack of a universal treatment to achieve urinary control. The aim of the study was to develop basic principles of surgical treatment of epispadias-related urinary incontinence. Additionally, we aimed to introduce into clinical practice the use of synthetic implants (synthetic slings) and evaluate treatment outcomes. The total of 20 boys aged 7–15 years received surgical treatment for subtotal and total epispadias. The first stage of surgical reconstruction was Cantwell's phallo-urethroplasty followed by the placement of synthetic slings TVT, TVT-O, and AdVance. The children began to accumulate up to 250–550 ml of urine in any position of the body at relative rest and on effort, and were able to hold urine for up to 3 hours and to empty the bladder completely with normal flow. The total loss of urine per day decreased 10-15 times and did not exceed 10–30 ml. The lower urinary tract was evaluated using urodynamic (uroflowmetry, urethral profilometry) and electrophysiological (electroneuromyography) methods. Restoration of urethral anatomy leads to improved accumulative ability of the detrusor, and use of synthetic slings is a low-invasive and highly effective surgical method for treating urinary incontinence.

Keywords: epispadias, boy, urethroplasty, sling, implant

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СИНТЕТИЧЕСКИЕ СЛИНГИ В КОМПЛЕКСЕ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ЭПИСПАДИИ У МАЛЬЧИКОВ

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Проблема лечения недержания мочи при эписпадии — пороке развития нижних мочевых путей — является наиболее сложной и актуальной в связи с тяжестью врожденных анатомо-функциональных нарушений и отсутствием универсального метода лечения, позволяющего в полной мере достичь управляемого акта мочеиспускания. Целью исследования была разработка основных принципов хирургического лечения недержания мочи при эписпадии и внедрение в клиническую практику имплантов (синтетических слингов) с последующей оценкой результатов лечения данного порока развития. Проведено оперативное лечение субтотальной и тотальной эписпадии у 20 мальчиков 7–15 лет. На первом этапе хирургической реконструкции выполнена фаллоуретропластика по методу Кантвелла (Cantwell), на втором — проведена имплантация синтетических слингов TVT, TVT-O, AdVance. Дети стали накапливать до 250–550 мл мочи в любых положениях тела, в состоянии относительного покоя и при напряжении удерживать мочу до 3 ч, полностью опорожнять мочевой пузырь по позыву нормальным потоком. Общие потери мочи в сутки уменьшились в 10–15 раз и не превышали 10–30 мл. Для оценки состояния нижних мочевых путей использовали уродинамические (урофлоуметрия, профилометрия уретры) и электрофизиологические (электронейромиография) методы исследования. Восстановление уретральной анатомии приводит к улучшению накопительной способности детрузора, использование синтетических слингов является малотравматичным и высокоэффективным хирургическим методом устранения недержания мочи.

Ключевые слова: эписпадия, мальчик, уретропластика, слинг, имплант

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Epispadias is a rare congenital malformation occurring in 1 in 100,000 births, with male : female ratio of 1 : 3.5 [1]

The most pronounced clinical symptoms of epispadias are urinary incontinence and absent urine output that force the child's parents to seek medical advice. Over the last 150 years, the efforts of the medical community have been focused on the search of effective surgical treatments to fully restore bladder function and stimulate its normal filling and emptying. The history of this search provides examples of incredible ingenuity [2–4]. Numerous publications demonstrated that most of the authors relied on isolated observations. Due to limited clinical experience and the use of a single surgical technique, the results of the intervention were unpredictable and often associated with poor outcome, so the problem remained unsolved. For a hundred years, the idea of surgical reconstruction and creation of an artificial sphincter mechanism using bladder tissues, autologous myofascial flaps or homografts did not materialize [2, 5].

It should be noted that in the middle of the XX century even time-proven variations of urethral sphincteroplasty were effective in no more than 50 % of cases. Half of the children received multiple surgeries. According to Derzhavin, who in 1962 proposed internal urinary sphincter reconstruction using the muscles of the urinary bladder trigone (the method is still used), 28 of 58 children with epispadias received revision surgeries. In N. E. Savchenko City Clinical Hospital, Derzhavin's and Young-Dees' methods were effective in 86.9 and 61.9 % of cases, respectively; however, 42 % of patients had revision surgeries [2].

Initially, the unsatisfactory results were attributed to failure to comply with the author's surgical technique. Another reason was discovered later. Epispadias is often accompanied by bladder hyperactivity and myelodysplasia associated with impaired innervation of the pelvic floor. It was found that an integral indicator of the severity of the structural and functional changes in the lower urinary tract of epispadias patients was the degree of pubic symphysis diastasis: a greater gap was associated with more severe bladder dysfunctions and innervation defects of the pelvic floor muscles and consequently with unsatisfactory results of traditional surgical treatment [6].

The doctors of the Department of Urology and Neurourology of the Scientific Research Institute of Pediatric Surgery have a 40-year experience in managing patients with epispadias. Throughout all these years, a need for fundamental changes in the traditional approaches to epispadias treatment has been gradually arising. It is believed that treatment should consist of several stages: urethral reconstruction followed by sphincterplasty and subsequent elimination of residual micturation disorders using minimally invasive techniques (paraurethral gel or collagen implantation); the final stage includes correction of cosmetic defects.

The aim of this study was to formulate the basic principles of a novel approach to surgical treatment of urinary incontinence in boys with epispadias based on the use of implants (synthetic slings) and to assess treatment outcomes.

METHODS

Since 2000, we have observed 20 boys of 7–15 years of age with epispadias (11 patients with subtotal form and 9 patients with total form). The main complaint was stress urinary incontinence, which appeared or increased as the abdominal pressure exceeded the intraurethral pressure.

The diagnosis of congenital malformation of the lower urinary tract was based on the clinical examination and standard and specialized test, such as intravenous urography, cystography, cystoscopy, uroflowmetry, and electrophysiological and urodynamic tests.

Clinical examination of boys left no doubts about the diagnosis of epispadias. Described in the literature in detail, the defect is obvious. A primary technique used to identify the defect is a standard physical examination sufficient to classify the disease as total or subtotal [2]. Further use of specialized techniques is necessary to detect concomitant renal and urinary tract defects and to assess the condition of the bladder and ureteral openings, pubic symphysis diastasis, sphincters and innervation of the pelvic floor muscles.

In the observed boys, the visible symptoms suggested a typical form of epispadias. In the supine and sitting positions, the children accumulated from 30 to 200 ml of urine in the bladder. The upright position led to increasing urinary incontinence aggravated by coughing and movement. The anterior wall of the urethra was cleft along the entire length; the external opening of the urethra had a funnel shape. Diastasis of pubic symphysis was 17.1–37.5 mm (compared to 7–8 mm in healthy individuals). In two cases during cystography bilateral grade II vesicoureteral reflux was detected; in one of them reflux was complicated by chronic pyelonephritis.

During cystometry, detrusor hyperreflexia was detected in 17 children. Electromyography revealed impairement of segmental somatic innervation in 11 children.

The severity of the pelvic floor dysfunction was evaluated by electroneuromyography and cough orthostatic profilometry, which helps to detect pelvic floor failure. Upon natural bladder filling possible with the child lying horizontally, uroflowmetry often registers a urodynamic dysfunction expressed as urgent urination.

After epispadias was diagnosed, Cantwell's phallourethroplasty was performed as the first stage of the treatment plan (Fig. 1).

Described in 1894, this surgical technique was used to reconstruct the urethra in an epispadias boy [7]. It is quite effective and solves the main task of the first stage, namely, the restoration of urethral anatomy. In males with epispadias, this urethroplasty option should be considered the procedure of choice.

The second stage was the implantation of synthetic slings: TVT (Tension-free Vaginal Tape), TVT-O (Tension-free Vaginal

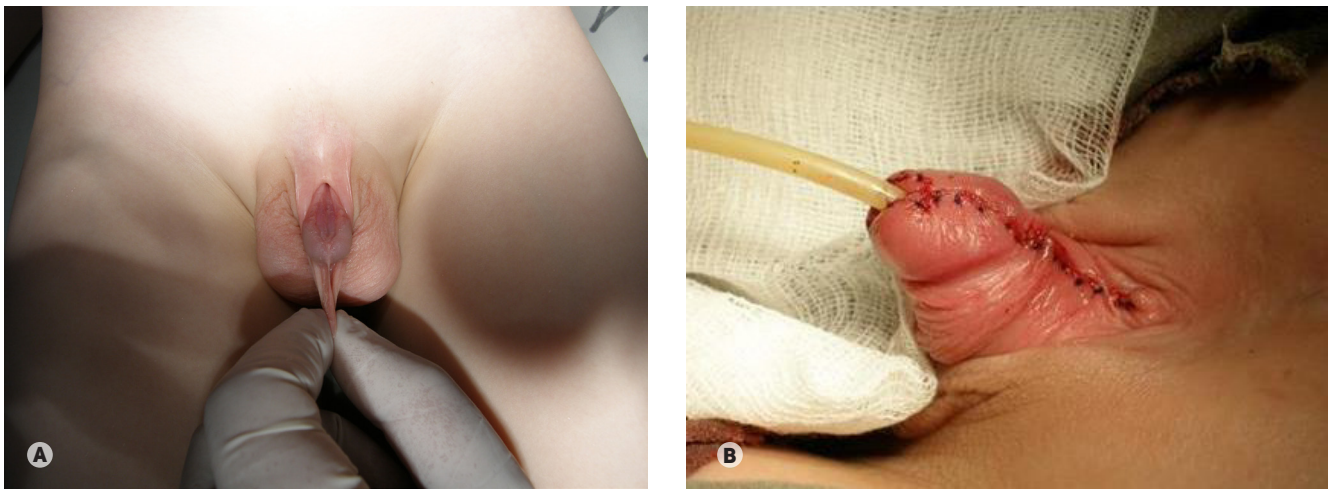


Fig. 1. Cantwell's phallourethroplasty: **(A)** penis before the surgery; **(B)** the final stage of the surgery, with Foley catheter Ch10 inserted

Tape Obturator) and AdVance performed as an independent minimally invasive technique.

Surgical technique. A semilunar incision was made across the perineum; the bulbous urethra was isolated down to the pelvic floor. Needles with a Prolene mesh tape were passed either side of the urethra through the obturator foramen to exit via skin incisions or guided through the retropubic space towards the anterior abdominal wall. The tape was positioned over the bulbous urethra and then pulled until urine leakage induced by an increase in abdominal pressure fully stopped. The following synthetic slings were used: GYNECARE TVT (Ethicon, Switzerland), GYNECARE TVT-O (Ethicon, Switzerland) and AdVance (AMS, USA). The Prolene tape ends were trimmed off and placed under the skin. The incisions were closed.

Postoperatively, the bladder was drained with a catheter for up to seven days. To prevent infectious complications, the antibiotic therapy was administered for 7 days.

We believe that in boys over the age of 10 with obvious pelvic floor prolapse, implantation of the AdVance sling is preferable, as it allows loop tensioning and creating a larger area of the controlled compression of the urethra.

Stages of the implantation of TVT-O (Fig. 2), TVT (Fig. 3) and AdVance (Fig. 4) slings are shown below.

RESULTS

Phallourethroplasty helped to restore the urethra completely in all the boys. However, in four children urethral fistulas were observed. In all cases, the fistula tract was suture ligated and fistulas were closed.

Thus, the reconstruction of urethra was successfully completed in 20 children with epispadias. The restoration of the urethral anatomy was accompanied by fundamental changes in the bladder function. The immediate and long-term (>5 years) result of the surgery was the crucial change in the urine transport through the lower urinary tract.

In all cases, the first phase of the micturation cycle (storage) was restored. Children began to accumulate up to 150–350 ml of urine in any positions of the body; as the bladder filled, the urge appeared; voluntary urination was characterized by normal flow and the absence of residual urine; the nature of urinary incontinence changed: it occurred when patients changed the position to vertical and after a sudden and sharp increase in intra-abdominal pressure (induced by cough, brisk walking, etc.). The total loss of urine per day decreased more than 5 times and did not exceed 50–370 ml.

Indications to loop sphincteroplasty, which is the second stage of surgical correction, were considered individually. The main criteria were the physical development of a child and the condition of tissues at the potential surgical site. In our experience, sphincteroplasty can be performed 6–12 months after the first stage of surgical treatment.

The choice of the sling should be based on the results of clinical and instrumental test. Both the amount of urine passed in the vertical position of the body (such as on exertion) and the degree of innervation impairment reflected by urodynamic parameters should be considered. The most important here is intraurethral pressure gradient measured by orthostatic profilometry (Fig. 5, 6).

Urethral pressure profilometry was performed using Delphis B-94-R01-BT Urine Analyzer (LABORIE, Canada).

In the 2–15-year follow up of the sling surgery, bladder capacity in the vertical position varied from 150 to 550 ml in all children. The boys were able to hold urine in any position of the body at relative rest or on effort up to 3 hours and emptied the bladder completely after getting the urge; the flow was normal and no residual urine was present. In 5 boys, total urine loss did not exceed 5–10 ml per day; 15 other children were completely continent. Reliability of the results derived from the good clinical effect, which allowed us to skip statistical data processing.

DISCUSSION

Regardless of the severity of the urethral cleft, penis deformities and other manifestations of the disease, the primary complaint that forces parents to seek medical advice of the urologist is child's urinary incontinence, the most obvious and bothersome symptom that affects both the child and his/her environment, which in turn can aggravate the disorder. Children and teenagers are particularly vulnerable, especially in certain "critical" periods of life when they undergo psychological and physiological changes (enter a new social environment - kindergarten, school, or adult society).

Although there are numerous publications on this problem, many controversial issues are yet to be discussed. One of them is the classification of the pathology. Classification of epispadias

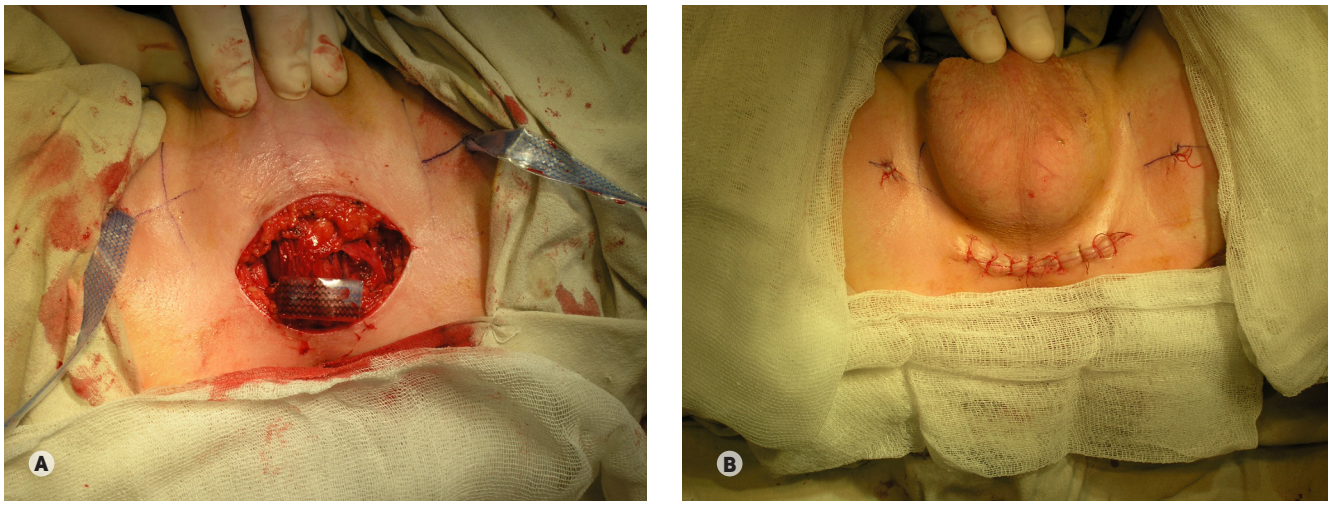


Fig. 2. Implantation of the TVT-O synthetic sling: **(A)** placement of the sling: the Prolene tape is placed under the bulbous urethra, the ends are brought out through the obturator foramen; **(B)** final appearance after the surgery: perineal skin sutures and tape exit sites

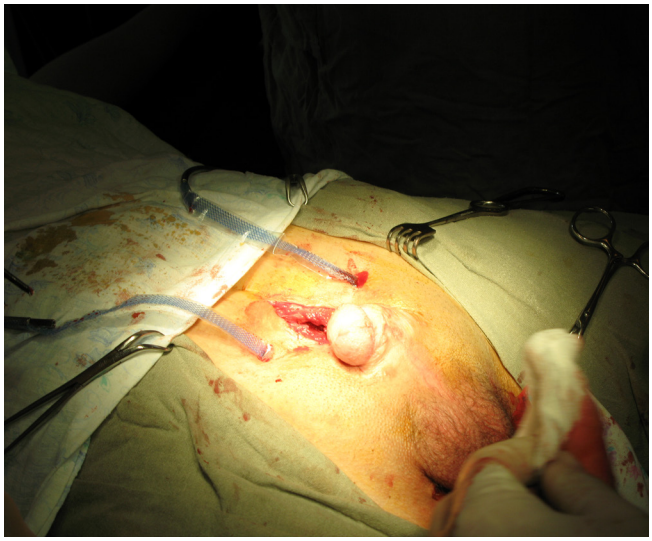
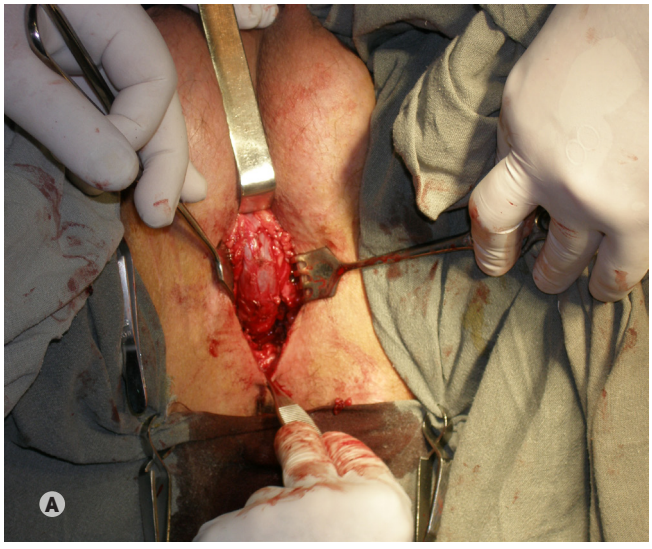


Fig. 3. Implantation of the TVT synthetic sling performed on a boy with epispadias: TVT tape exit sites on the anterior abdominal wall



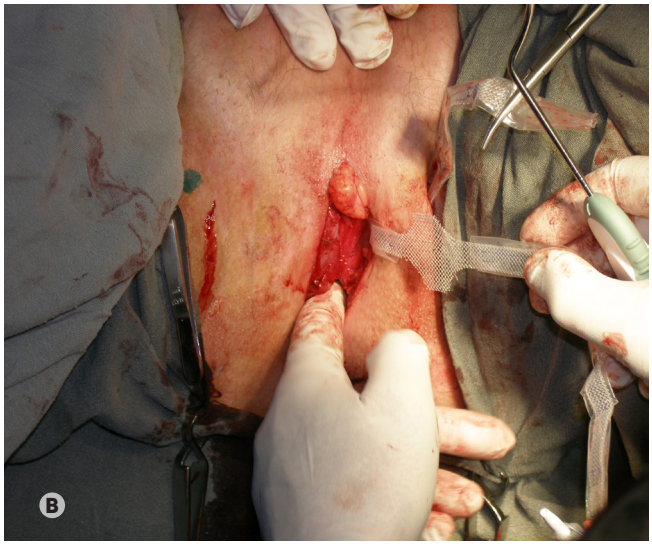


Fig. 4. Implantation of the AdVance synthetic sling. **(A)** the bulbous urethra is isolated; **(B)** preparing to fix the synthetic tape over the urethra

The sling is placed over the bulbous urethra and pulled until urine leakage induced by an increase in intra-abdominal pressure fully stops.

by Savchenko and Derzhavin published in 1976 is considered to be the most comprehensive [2]. However, its practical value with regard to the choice of treatment is minimal.

The most prominent results were obtained by Derzhavin who in 1962 proposed the internal sphincter plasty using the muscles of the urinary bladder trigone [8]. It is still considered one of the most effective methods of surgical correction of urinary incontinence in epispadias.

The choice of surgical techniques for urinary incontinence treatment in epispadias patients should be based on the detailed analysis of the anatomical and functional properties of the defect [9, 10].

Before the surgery, the surgeon faces a difficult task — the choice of surgical technique, and they have to decide whether to start with urethroplasty or sphincteroplasty. In our experience, it is reasonable to restore the integrity of the lower urinary tract first, i.e. to perform urethroplasty. There are a lot of surgical techniques for urethroplasty that can be performed on males and females with various malformations of the external genitalia.

The Cantwell technique for treating epispadias in men has been proved to be one of the most effective [7]. It was successfully applied during the surgery on an 11-year-old boy with epispadias and described in May, 1894. In addition to restoring the anatomy of the urethra, the surgery restored voluntary urination. From our observations a firm conclusion can be made that not only the sphincter apparatus of the bladder, but also the urethra is involved in the complex mechanism of continence.

The surgical correction of incontinence in the “sphincters-pelvic floor” system is based on the use of the so-called loop surgeries. In the second half of the 20th century, loop (sling) surgeries were introduced into pediatric practice based on the use of autologous tissue: free muscle, fascial, skin or vaginal flaps, vascularized muscular, aponeurotic or muscular-aponeurotic segments of the rectum, pyramidal or oblique muscles of the anterior abdominal wall, the tensor fasciae latae muscle, and gluteal muscles [11, 12].

Since 1989, we have been using various autologous tissues, mainly vascularized muscular-aponeurotic flaps of the rectum and pyramidal muscles of the anterior abdominal wall. However, the lack of efficacy in long-term periods (over 2-3 years) forced us to continue the search for materials that could be used for surgical treatment of urinary incontinence [13]. At some point, we used velour vascular grafts. Then, a new method for treating stress urinary incontinence in women was suggested: implantation of the free synthetic loop (TVT); the tape was passed through the retropubic space and brought up to the abdominal skin incision. The technique was suggested by Ulmsten and Petros in 1990 and was based on the idea of urethral occlusion on exertion resulting from the contraction of the anterior abdominal wall muscles [14–19]. In 2000 our clinic pioneered the use of a new implant type, synthetic slings, in children. Later in 2002 and 2003, modifications were proposed to the technique: the Prolene tape was passed through the obturator foramen (TOT and TVT-O surgeries) [3, 20–22]. In 2006, a new sling technology, AdVance, was introduced into clinical practice. Our clinic was the first in the Russian Federation to suggest the use of Prolene tapes (TVT, TOT, TVT-O; AdVance) for surgical treatment of stress urine incontinence in children of both sexes with malformations and pelvic floor innervation impairments.

Among the advantages of this medical technology over other pediatric surgeries, such as myofascial loop surgery, are minimal invasiveness (it is less traumatic, faster and allows for

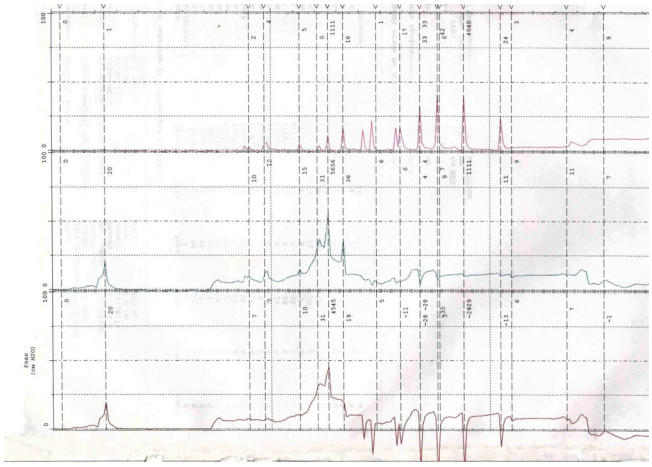


Fig. 5. Patient Ch., 8 years. Cough urethral pressure profile prior to sling surgery
Reduction of urethral pressure gradient to 40 cm water (normal values are 70–100 cm water), significant pressure reduction on exertion.

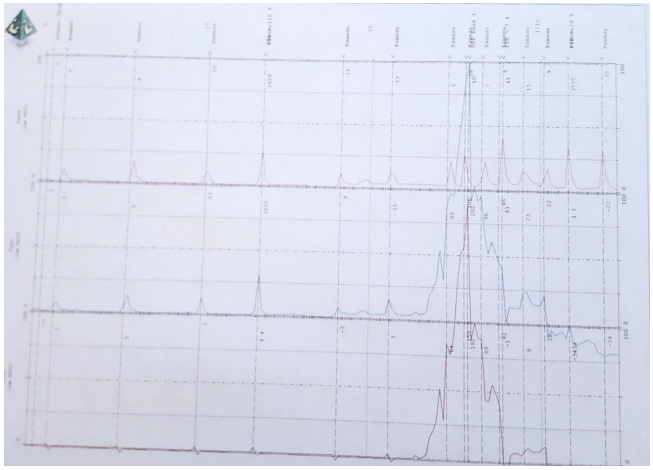


Fig. 6. Patient Ch., 8 years. Cough urethral pressure profile 12 months after sling surgery
Urethral pressure gradient is 100 cm water, with high gradient of pressure profile on exertion.

a shorter postoperative rehabilitation period), higher efficacy and simplicity.

Multiple causes and the exceptional complexity of pathogenic mechanisms and clinical symptoms in epispadias demand sufficient rationale for surgical exposure in patients with incontinence. Full control over urination in children with epispadias is hard or sometimes impossible to achieve [23–26]. This proves once again that surgical correction of the defect should be performed in the following sequence: urethroplasty → sphincteroplasty → elimination of residual urination disorders → improvement of cosmetic defects.

One should always be aware of surgical failures when urinary incontinence is formally retained [6]. Classification of this pathology is also an issue. Currently, we differentiate between imperative, stress, combined and overflow urinary incontinence. All these forms of incontinence are found in epispadias and can be used as a criterion when deciding on treatment strategies. In some of our observations, we saw that imperative incontinence, which was erroneously attributed to the failure of the reconstruction of the sphincter apparatus, was easily eliminated with medication therapy. Thus, revision surgery was no longer necessary in those cases. Before deciding on revision surgery, the clinical form of the pathology and causes of incontinence must be identified.

After detrusor function has been restored, we can proceed to the next treatment stage. In cases of isolated lesions of the sphincter apparatus and weak pelvic floor (sphincter deficiency) the abdominal pressure is higher than the pressire inside the urethra, which results in stress incontinence [27]. The typical symptom here is loss of urine on effort or exertion (such as coughing, laughing, changing body position, lifting objects, etc.); it helps to assess indications for sling surgeries.

Based on our experience, the following indications for sling surgeries were formulated:

– intractable urinary incontinence on exertion;
– sufficient bladder capacity (at least 150 ml);
– low pressure inside the bladder in the storage phase (under 20 cm water);
– low profile of intraurethral pressure;
– negative cough test;
– positive external compression test of the urethra;
– minimal changes in the urodynamics of the upper urinary tract.

It is possible that in some cases minimally invasive technologies (paraurethral administration of bulking agents) or pharmacotherapy may determine treatment outcome.

To assess the effectiveness of surgical treatment of urinary incontinence in children, we used the following criteria: urine continence for 1.5 h or longer at different body positions and on exertion; restored voluntary urination (if possible) characterized by sufficient urine flow in the absence of residual urine.

No complications, such as sling displacement, were observed for any type of synthetic slings (TVT, TOT, TVT-O; AdVance) used in this study [28].

CONCLUSIONS

For surgical treatment of urinary incontinence in boys with epispadias, a stage-by-stage approach should be applied, the first stage being phallourethroplasty followed by the sling surgery after the detrusor has restored its capacity and the ability to adapt to changing urine volume. For the second stage, the use of synthetic slings is recommended.

The main urodynamic indicator of the weakened pelvic floor is urethral profilometry data.

High pressure inside the bladder and the urodynamic disorders of the upper urinary tract are contraindications to sling surgery.

To summarize, we have carried out surgical treatment of boys with anatomical defects and urinary incontinence resulting from sphincter deficiency upon restoration of bladder storage function involving implantation of different sling types (we recommend synthetic materials). Complex and reliable evidence required for deciding on treatment strategies ensured positive outcomes including control over urination in most patients with epispadias and helped to minimize the number of revision surgeries. Coupled with improvement of cosmetic defects, this allowed the patients to successfully socialize and achieve a high quality of life.

Surgical treatment of such rare malformations as epispadias should be carried out in specialized surgical centers.

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TWO-STAGE REPAIR OF FINGER FLEXOR TENDONS IN CHILDREN WITH CHRONIC TENDON RUPTURES IN FIBRO-SYNOVIAL CANALS

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Two-stage repair is a well-developed method that is commonly used to repair chronic ruptures of flexor digitorum profundus tendons. However, its use in pediatric hand surgery is limited due to the absence of tendon implants adapted for children. The article describes a modified Paneva-Holevich/Hunter technique for two-stage tendon reconstruction using original, oval, Lavsan-reinforced silicone prosthetic implants of four sizes (depending on patients' age). The surgery was performed in 34 children aged 1.5–17 years. Long-term outcomes were assessed in 12 patients (8 boys and 4 girls) using the Total Active Motion scale. The follow-up period was 30 months. The average active range of motion accounted for 178.8° in boys and 218.8° in girls. The results of treatment (TAM %) were considered good in all the girls (average score of 84.3 %), and in those boys who received surgery for fingers IV and V (average score of 80.0 %). The boys who received tendon repair for fingers II and III had "good" and "poor" results (average score of 67.0 %). The proposed method of two-stage tendon repair of chronic tendon ruptures in fibro-synovial channels in children was shown to provide good results with minimal complication rates and acceptable donor site deficiency.

Keywords: two-stage tendon repair, tendon silicone prosthetic implants, tendons of flexor digitorum profundus, chronic ruptures

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ДВУХЭТАПНАЯ ТЕНДОПЛАСТИКА СУХОЖИЛИЙ СГИБАТЕЛЕЙ ПАЛЬЦЕВ КИСТИ У ДЕТЕЙ С ЗАСТАРЕЛЫМИ ПОВРЕЖДЕНИЯМИ В ЗОНЕ ФИБРОЗНО-СИНОВИАЛЬНЫХ КАНАЛОВ

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Двухэтапная тендопластика — хорошо разработанный метод лечения застарелых повреждений сухожилий глубоких сгибателей пальцев кисти, однако его применение в детской кистевой хирургии ограничивается отсутствием адаптированных для детей эндопротезов сухожилий. В статье описана модификация метода двухэтапной тендопластики Паневой-Холевич и Hunter с использованием оригинальных силиконовых эндопротезов овального сечения, армированных лавсановой лентой, четырех типоразмеров, соответствующих различным возрастным группам. Были прооперированы 34 ребенка в возрасте 1,5–17 лет, у 12 из них (8 мальчиков и 4 девочек) были оценены отдаленные результаты лечения по шкале Total Active Motion (срок наблюдения — 30 мес.). Средний активный объем движений поврежденного пальца в группе мальчиков составил 178,8°, в группе девочек — 218,8°. Хорошие результаты лечения (TAM %) были отмечены у всех девочек (в среднем 84,3 %), а также у мальчиков, которым оперировали IV и V пальцы (в среднем 80,0 %). У мальчиков, которым оперировали II и III пальцы, наблюдали хорошие и плохие результаты (в среднем 67,0 %). Предложенный метод двухэтапной тендопластики при застарелых повреждениях сухожилий в области фиброзно-синовиальных каналов у детей позволяет достичь хорошего результата с минимальными осложнениями и приемлемым донорским дефицитом.

Ключевые слова: двухэтапная тендопластика, сухожильные силиконовые эндопротезы, сухожилия глубоких сгибателей пальцев кисти, застарелые повреждения

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Chronic ruptures of the flexor digitorum profundus tendons in children remain a pressing issue of pediatric hand surgery. This is a relatively uncommon injury [1], but its consequences are extremely negative for children. Long-term results of treatment remain unsatisfactory for a number of reasons: complexity of the initial diagnostic assessment, a large number of missed tendon injuries (up to 30 %); a small diameter of tendons, which hinders the use of multifilament sutures and does not allow the reconstructed tendon to achieve the desired strength. In addition, the lack of cooperation and motivation in young patients precludes early active rehabilitation [2, 3].

The most challenging is the injury of flexor digitorum tendons in zone 2. This zone extends from the distal palmar crease (proximal end of the first annular ligament, or A1 pulley) to the middle of the middle phalanx. In this zone flexor digitorum superficialis and flexor digitorum profundus tendons criss-cross and glide into a narrow fibro-synovial canal. Injuries in zone 2 are associated with a high risk of scarring after surgical repair, which prevents normal sliding of tendons [4–6]. Bunell [7] called this zone “critical” and “no-man's-land” (Fig. 1).

Two-stage repair is a well-established method of flexor digitorum profundus tendon repair in cases of extensive scarring in the area of the fibro-synovial canal. Various modifications of this method have been proposed [8–17]. However, the use of this method in pediatric hand surgery is impeded due to the absence of prosthetic implants adapted for children. Using our experience in tendon repair according to Paneva-Holevich [9, 10] and Hunter [8, 12] techniques, we have developed an original method of two-stage repair with silicone oval Lavsan-reinforced implants (developed jointly with Medsil, Russia). The implants are available in four sizes for children of different age. The use of these implants allows for the adaptation of the existing protocols of postoperative passive and active rehabilitation for children. Currently, a state patent for these implants is being filed.

The aim of the study was to assess the efficacy of treatment of chronic flexor digitorum profundus tendon ruptures in children using a modified two-stage repair and original implants.

METHODS

In 2010–2016, in the Department of Reconstructive Microsurgery of N. F. Filatov Children’s Municipal Clinical Hospital No. 13 (Moscow), there were 34 patients aged 1.5 to 17 years with chronic ruptures of flexor digitorum produndus tendons in the fibro-synovial canal. Most tendon injuries were caused by knives (n = 18), an edge of a metal fence (n = 11) and glass (n = 5). The time of injury was approximately 54–90 days before admission.

Two-stage repair of flexor digitorum profundus tendons was performed in all children. At the first stage we used a Brunner zigzag skin incision (Fig. 2) that provided wide access to the fibro-synovial canal. The canal was opened; scar tissues and tendon remnants were excised. A-2 and A-4 pulleys were retained or reconstructed. As opposed to Paneva-Holevich and Hunter techniques, the proximal stumps of the flexor digitorum superficialis and flexor digitorum profundus tendons were retrieved and then sutured side-to-side and to the fibrous tissues with moderate tension at the base of the proximal phalanx. This enabled us to increase elasticity, improve the contractile function of the injured flexors, and avoid the “muscle tenotomy” effect. A silicone prosthetic implant was placed under the retained or repaired pulleys. Its distal end was fixed to the distal phalanx under the stump of the flexor digitorum profundus tendon, and the proximal end was placed freely under the flexor tendons on the palm (Fig. 3). For immobilization, the patients wore the dorsal plaster splint for 4 weeks. Passive range of motion exercises were started to achieve the full range of passive flexion immediately after the first stage of repair.

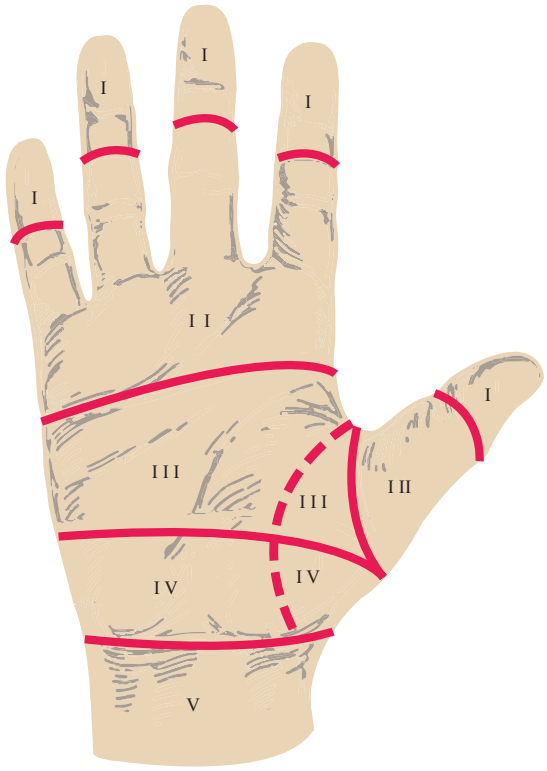

Fig. 1. Location of zone 2 (no man’s land)

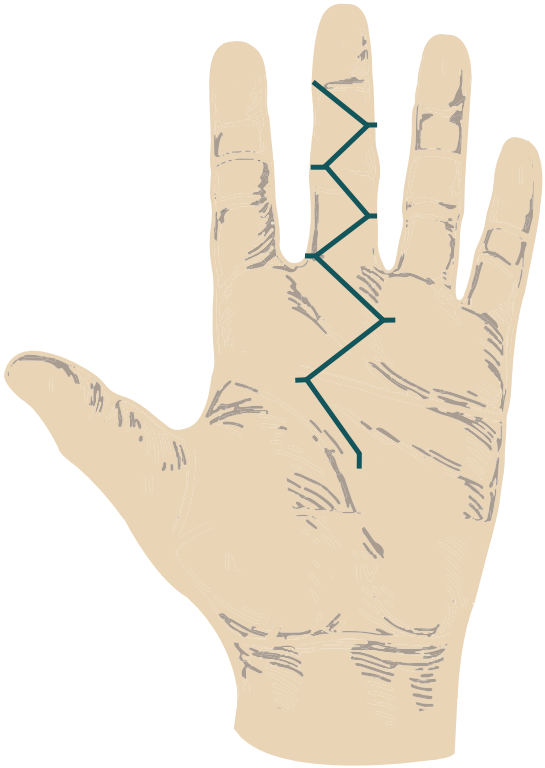

Fig. 2. Brunner zigzag incision

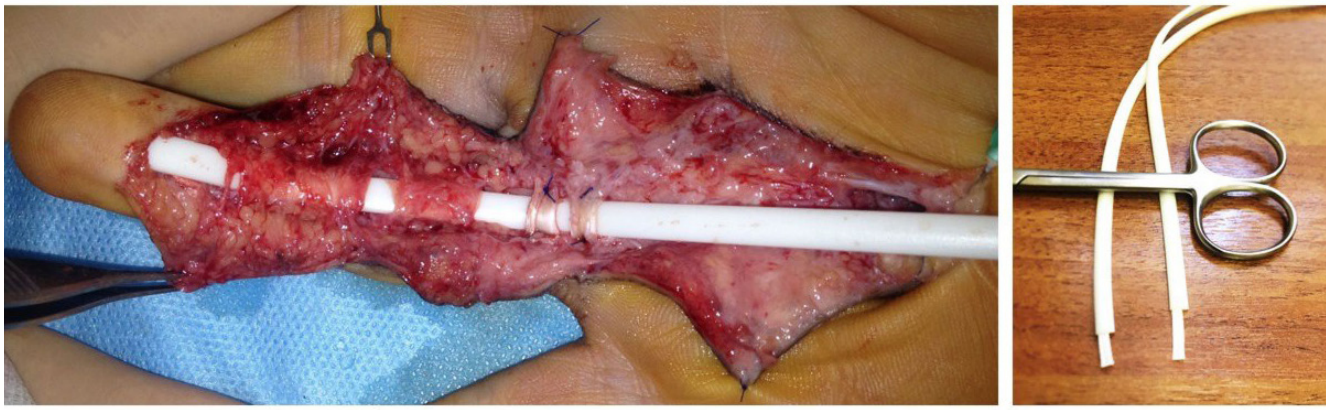

Fig. 3. The first stage of flexor digitorum profundus tendon repair: fixation of the silicone prosthetic implant

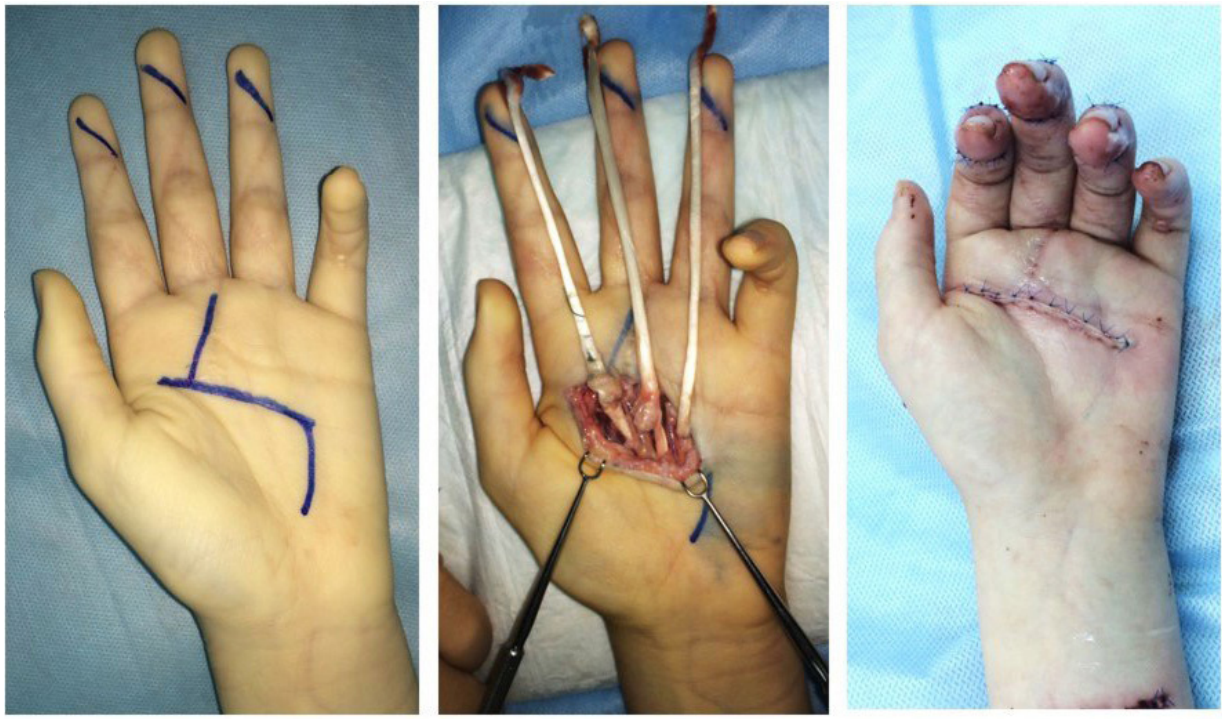

Fig. 4. The second stage of flexor digitorum profundus tendon repair: fixation of the autograft

The second stage of repair was performed 2–2.5 months later. Incisions were made in the distal phalanx, palm and middle third of the forearm (Fig. 4). The flexor digitorum superficialis tendon was retrieved from the middle third of the forearm, cut and transferred to the palm. Using the prosthetic implant as a guide, the autograft was passed through the canal to the distal phalanx and fixed transosseously. The excess of the fibro-synovial canal was dissected proximally to allow free movement of the autograft. Proximal tendon suturing was performed using the Pulvertaft technique. The graft tension was adjusted so that the repaired finger was at less angle of flexion than adjacent ulnar finger.

In the postoperative period, patients wore the dorsal plaster splint (flexion at the radiocarpal joint was 30°, flexion at the metacarpophalangeal joints was 70°) for 5 weeks. Range of motion exercises and physiotherapy were started on day 3 after the surgery. We used early active-passive mobilization in our rehabilitation program.

The results of treatment were assessed with the scale (Total Active Motion) scale. The total range of motion was determined as the sum of the angles of active flexion in the operated finger joints. The score was calculated as the ratio of the damaged finger TAM to the healthy finger TAM multiplied by 100 %. A score of 100 % was considered “excellent”; a 75–99 % score was considered “good”; a 50–74 % score was considered “satisfactory”, less than 50 % score was considered “poor”. The long-term results were evaluated in 12 of 34 patients (30 months of the follow-up).

RESULTS

Table shows the long-term results of treatment of 12 children with chronic ruptures of flexor digitorum profundus tendons measured by the range of active motion using the TAM scale. According to the absolute TAM value, the active range of motion was by 40° greater in boys than in girls. Excellent results were seen in boys who had received repair of finger tendons IV and V (average score of 80 %), good and poor results were seen in patients who had received repair of finger

Long-term results of surgical treatment of children with chronic ruptures of flexor digitorum profundus tendons by two-stage repair using tendon silicone prosthetic implants (assessed with Total Active Motion scale)

No.	Age	Finger	TAM°	TAM %
Boys				
1	3.0	III	115.0	44.0
2	3.0	II	210.0	67.0
3	3.3	III	180.0	69.0
4	4.0	IV	190.0	79.0
5	5.0	IV	185.0	86.0
6	12	II	195.0	72.0
7	15	V	195.0	75.0
8	17	II. III	160.0	44.0
M	7.8	–	178.8	67.0
Girls				
9	2.3	IV	200.0	81.0
10	4.0	II. III	195.0	75.0
11	4.5	V	230.0	85.0
12	12	III	250.0	96.0
M	5.7	–	218.8	84.3

tendons II and III (average score of 67 %). Good results (84 %) were observed in all girls.

DISCUSSION

Two-stage repair of chronic ruptures of flexor digitorum profundus tendons in adults is a well-established method with detailed postoperative rehabilitation protocols. However, this method has not been properly adapted for children. A characteristic anatomical feature of children is a small size of the flexor tendons and the fibro-synovial canals. In addition, young children have a low ability for cooperation. We believe that our original Lavsan-reinforced tendon silicone prosthetic implants matching patients' age allowed us to successfully adjust the existing protocols of postoperative rehabilitation to low cooperative abilities of children.

CONCLUSIONS

A modified two-stage repair with the original tendon silicone prosthetic implants, adaptation of rehabilitation protocols to the behavioral characteristics of children, and close postoperative monitoring provided good long-term results of treatment regardless of patients' age and sex.

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APPLICATION OF THE BALLOON SKIN EXPANSION METHOD IN PEDIATRIC RECONSTRUCTIVE SURGERY

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The article describes the treatment of children with vast scar deformities and extensive benign soft tissue neoplasms. The method is presented in a clinical case of successful skin restoration using balloon skin expansion. The opinion and recommendations of the authors on optimal treatment of these defects and decrease of possible complications using laser Doppler flowmetry for evaluation of the state of microcirculation in the skin flap are based on the results of the long-term use of this method in the Department of Reconstructive and Plastic Microsurgery of Filatov Children's Municipal Clinical Hospital No.13.

Keywords: balloon skin expansion, soft tissue expander, expansion, scaring alopecia, skin grafting

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ПРИМЕНЕНИЕ МЕТОДА БАЛЛОННОЙ ДЕРМАТЕНЗИИ В ДЕТСКОЙ РЕКОНСТРУКТИВНО-ПЛАСТИЧЕСКОЙ ХИРУРГИИ

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В статье описана методика лечения детей с обширными рубцовыми деформациями и объемными доброкачественными новообразованиями мягких тканей на примере клинического случая успешного восстановления кожного покрова с помощью метода баллонной дерматензии. Мнение и рекомендации авторов об оптимальном лечении подобного типа дефектов, а также о снижении числа возможных осложнений при использовании лазерной доплеровской флоуметрии для оценки состояния микроциркуляции в кожном лоскуте основаны на результатах многолетнего применения данного метода в условиях отделения реконструктивной и пластической микрохирургии ДГКБ № 13 им. Н. Ф. Филатова.

Ключевые слова: метод баллонной дерматензии, тканевый эндоэкспандер, экспансия, рубцовая алопеция, кожная пластика

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The method of balloon skin expansion, first proposed by an American scientist C. Newman in 1957, has been successfully used in plastic and reconstructive surgery. The method is based on such properties of normal soft tissues and skin as elasticity and growth potential. It was described by a number of Russian and international authors. The scientists showed the advantages of this method [1–6].

An expander is a device for temporary implantation under the skin, which increases and stretches when filled with fluid. After attaining enough tissues, the expander is removed and the obtained stock of tissues is used for grafting. Expanders differ by size, profile, shape (round, oval, rectangular, in the form of a half-moon) and volume to which they can stretch. All expanders, both domestic and foreign, have a certain mandatory set of constructional elements and consist of biocompatible materials — silicone or latex. A balloon formed by a thin elastic membrane (smooth or textured) and a filling valve are compulsory constructional elements of expanders. The volume of the expander varies from 3 to 2000 ml. There are expanders with a high and low profile and with a strengthened base which allows stretching tissues in strictly given direction. Expanders with textured surface have a number of advantages: the fibrous capsule formed around them is more elastic; they do not shift and have a built-in valve. Comparing intratissue expanders in use, it may be noted that latex ones have a higher expansibility degree, while silicone expanders have higher strength properties with virtually the same biological response of surrounding tissues to both materials [1, 3–10].

Recently, the balloon skin expansion method has been widely used in pediatric plastic surgery for treatment of cicatrical deformities in the area of face, neck, trunk and limbs. Patients with benign neoplasms of complicated anatomical

location constitute a sizable group of patients in which a single-stage radical surgical removal of the neoplasm cannot always be performed. Therefore, such patients need long-term staged treatment frequently resulting in forming vicious cicatrix of soft tissues replacing tumor tissue. A separate group of patients is composed of children with cicatrical alopecia arising from injuries, burns or purulent inflammations. Cicatrical defect and cicatrical alopecia are serious cosmetic issues causing a patient constant distress, and in adolescence they provoke disturbance of social adaptation of a child among peers [3–5, 10].

For now, many morphological, histological and functional aspects of tissue endoexpanders have been studied. The studies of stretched skin flaps carried out in animals and humans showed that minor changes occurred in epidermis during tissue stretching. Using laser Doppler flowmetry, it was found that during expansion in the process of stretching, skin perfusion did not decrease but on the contrary did increase. This indicates that skin vessels participate in expansion. It is very likely that the vascular system is the main factor determining the degree of soft tissue stretching. Blood supply in a flap formed using the expander is effected on account of increase of vascularization of border zones and neoformation of vessels in the flap, their adaptation to stretching and formation of a vascular-fibrous capsule. In as little as several days after start of expansion, increase in the number of arterioles and venules occurs [1–5, 11–13].

The method of balloon skin expansion has been used in the Department of Microsurgery of of Filatov Children's Municipal Clinical Hospital No.13 since 1993. A solid experience has been accumulated in treatment of patients with alopecia, deformities, and skin and soft tissue congenital abnormalities. Additional instrumental methods of control of the state of the skin flap above the expander has been developed and embedded in practice, a mathematical method of calculation of the area of each flap has been developed which led to decrease in the number of complications and expansion time. 53 patients at the age from 1 month to 17 years were treated in the Department. Among them were 23 children (15 girls, 8 boys) with posttraumatic alopecias of the hairy part of the head, 19 children (12 girls, 7 boys) with extensive benign neoplasms of soft tissues, and 11 adolescents with scrotum hyperplasia.

Clinical case

A female patient Sh., 5 years old, was admitted to the Department of Microsurgery of Filatov Children's Municipal Clinical Hospital No.13 with soft tissue necrosis of the parieto-occipital area.

The child was bitten by a dog 1 month before admission. The initial surgical debridement of the wound of the parieto-occipital area was performed in a primary care facility. Later the necrosis of the skin flap of the parieto-occipital area developed (Fig. 1). In the Department of Reconstructive and Plastic Microsurgery, the necrectomy and free dermatoplasty were performed (Fig. 2).

As a result of the treatment, the wound defect was fully closed, the free skin flap showed signs of full recovery; however, later alopecia of the parieto-occipital area was formed with the size of 15.0 × 15.0 cm (Fig. 3, 4).

Six months later the tissue latex endoexpander was implanted. The endoexpander was manufactured in the Scientific Research Institute of Rubber and Polymer Goods (Russia) (Fig. 5). Filling of the expander began on postoperative day 14 after removal of sutures. The expansion was carried out using 10–20 ml sterile saline solution 2 times a week under control of laser Doppler flowmetry. Two months after installation of the expander, when maximum volume was achieved and the required stock of plastic material was formed, surgical treatment was performed — the removal of the tissue endoexpander and skin grafting with local tissues. As a result of the treatment, we managed to eliminate the alopecia patch in the right parietal region (Fig. 6).

Subsequently, the balloon skin expansion was repeated twice in this patient, and 1.5 years after the start of the treatment, the alopecia in the parieto-occipital region was fully eliminated (Fig. 7, 8).

DISCUSSION

The cosmetic result of treatment was evaluated as good. The alopecia patch was fully eliminated. Postoperative scars were normotrophic. Turgor and sensitivity of the skin flap above the expander were retained.

Application of tissue expanders in each patient requires accurate preoperative planning in selection of shape, size, profile, expander volume and the number of expanders. It is necessary to assess localization, size and configuration of a skin lesion subject to excision, to choose nearby zone or zones of normal soft tissues which expansion will allow achieving an excess sufficient for transplantation in the form of a local flap and closing of a tissue defect without tension. It is necessary to make sure that scar tissue incapable of stretching and growing adequately does not get into a zone of planned expansion; otherwise it will lead to non-uniform skin expansion, suture line disruption, exposal of the expander and development of local infection. It is also important that a surgeon should take into account individual skin traits of a patient in advance [1, 2, 6, 11, 12, 14, 15].

Tissue necrosis over the expander is one of the most frequent complications of the described method. The skin expansion under control of laser Doppler flowmetry may decrease the number of such complications. Using laser Doppler flowmetry, it was found that the indices of perfusion oxygen saturation in blood and specific consumption of oxygen in tissues increase

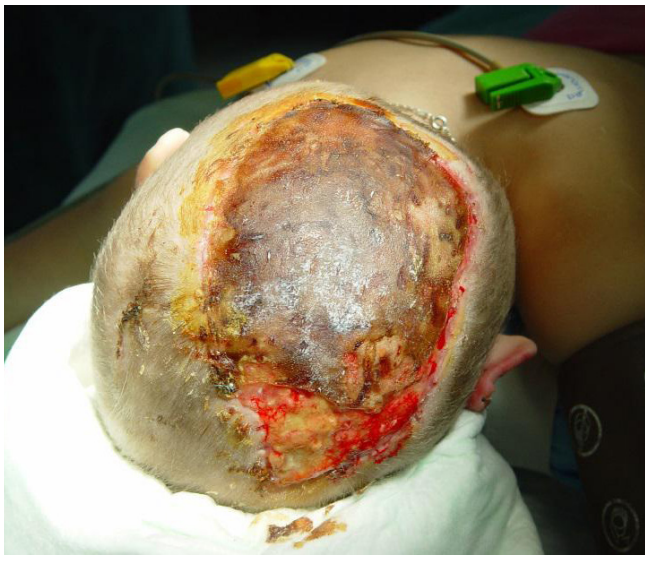

Fig. 1. Female patient Sh., 5 years old. Necrosis of the skin flap of the parieto-occipital area

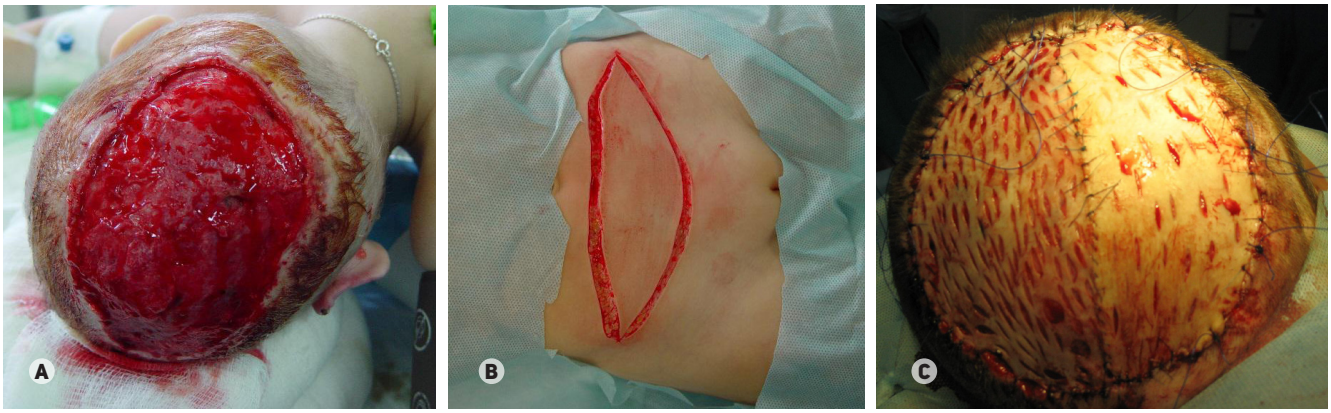

Fig. 2. Female patient Sh., 5 years old. Surgery stages: **(A)** Removal of the necrotic skin flap of the parieto-occipital area.; **(B)** Free skin grafting from the anterior abdominal wall; **(C)** the wound defect is fully covered with the skin flap

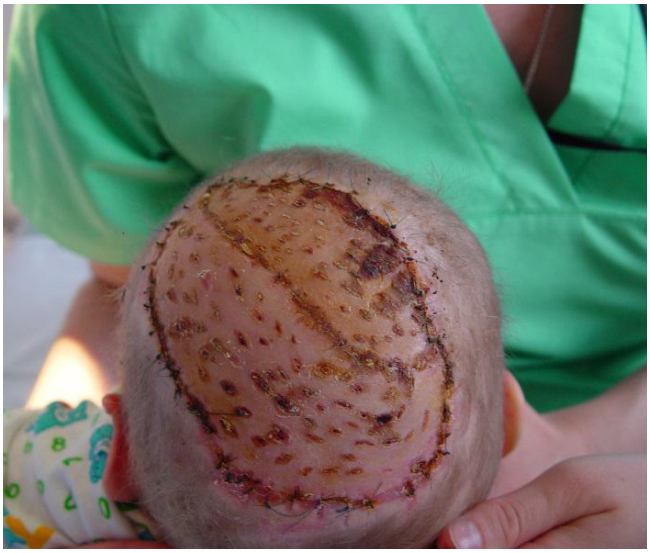

Fig. 3. Female patient Sh., 5 years old. Clinical photograph taken 14 days after surgery. The wound defect is fully closed, the full engraftment is observed

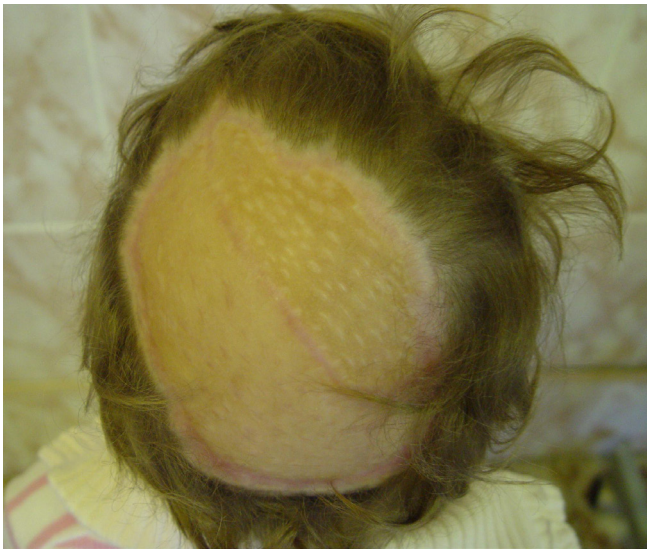

Fig. 4. Female patient Sh., 5 years old. Alopecia of the parieto-occipital region

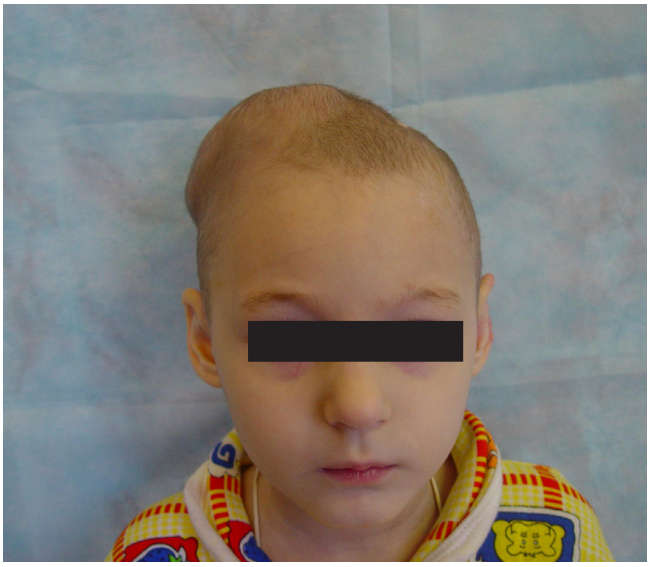

Fig. 5. Female patient Sh., 5 years old. The tissue endoexpander implanted in the right parietal region

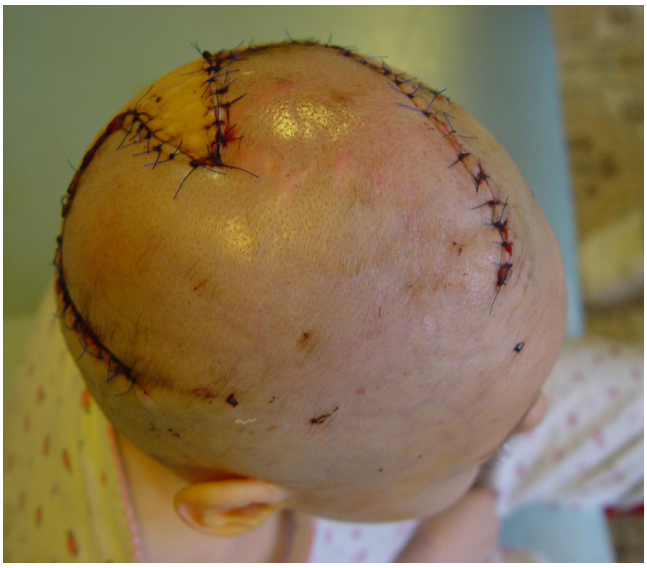

Fig. 6. Female patient Sh., 5 years old. Clinical photograph after elimination of alopecia in the right parietal region

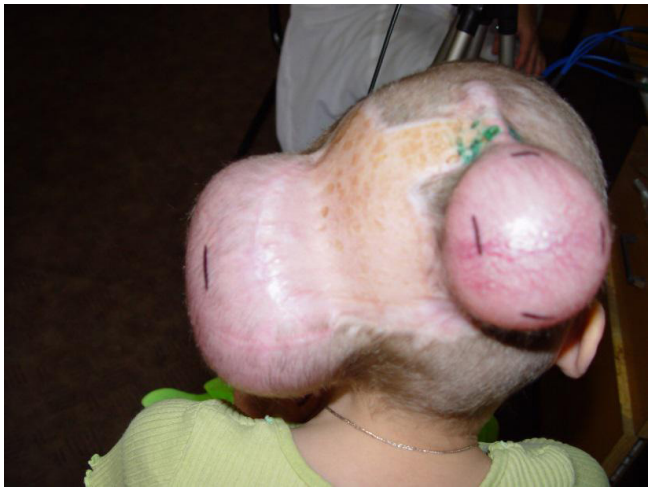

Fig. 7. Female patient Sh., 5 years old. Clinical photograph after implantation of two tissue endoexpanders

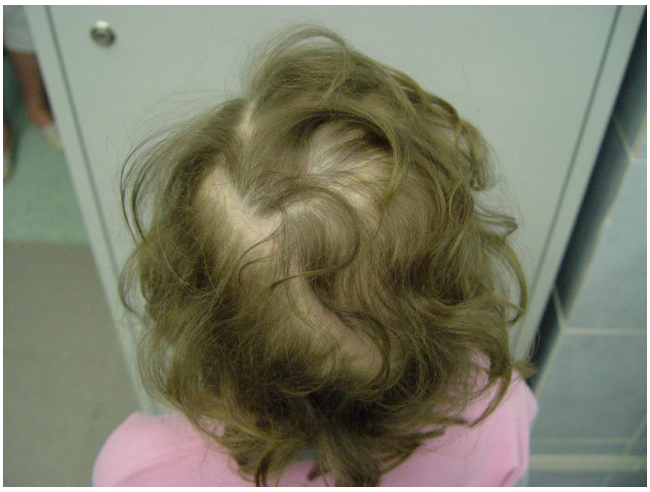

Fig. 8. Female patient Sh., 7 years old. Clinical photograph taken 1.5 years after treatment

during expansion regardless of shape and size of the expander as well as of its localization and the number of endoexpanders implanted in the same anatomical region [1, 2, 4, 5, 15, 16].

CONCLUSIONS

There are different options of surgical repair of skin and surrounding tissues: local flap grafting, local grafting with triangular flaps, free skin grafting, combined skin grafting. However, such procedures may be very complicated and challenging, and are often poorly tolerated by patients and require the involvement of another skin region. Balloon skin expansion method is more efficient and should be considered an optimal technique of skin recovery. The laser Doppler flowmetry can be used for the monitoring of the microcirculation in the skin flap above the expander to prevent possible complications.

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THE EFFICACY OF SYSTEMIC ENZYME THERAPY IN THE COMPLEX TREATMENT OF TROPHIC ULCERS OF VENOUS ETIOLOGY

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The current strategy for the treatment of venous trophic ulcers (VTU) suggests differentiated approach and a combination of conservative and surgical methods. This paper presents the results of the study of efficacy of systemic enzyme therapy (Phlogenzym by Mucos Pharma, Germany) in patients with varicose veins of lower extremities (CEAP class C6) and stage I, II and III VTU. The study included 38 patients aged 12 to 82 years. The patients were divided into the experimental (n = 20) and the control (n = 18) groups. The treatment lasted 1 month. Silcofix Professional wound dressings (Pharmaplast, Egypt) were used. All patients received Detralex (Les Laboratoires Servier, France) and wore class 2 and 3 knee-high compression socks. Patients of the experimental group also received Phlogenzym for 30 days (3 tablets 3 times a day). Total ulcer epithelization was observed in 8 (40 %) patients by week 3, and in 18 (90 %) patients by the end of treatment compared to 4 (22 %) and 9 (50 %) patients in the control group, respectively. In the control group, the regenerative process in the area of the ulcerous defect was less prominent compared to the experimental group. Immunoassays revealed a significant reduction in $CD4^+CD25^{Bright}$ cells and increased levels of $CD4^+CD45RO^+$ T-lymphocytes in the experimental group, corresponding with the observed positive clinical response. The use of immunomodulatory drug Phlogenzym contributed to a more rapid regression of clinical symptoms of chronic venous insufficiency and faster healing of stage I–III venous trophic ulcers.

Keywords: varicose veins of lower extremities, venous trophic ulcer, adaptive immunity, lymphocyte subpopulation

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ЭФФЕКТИВНОСТЬ СИСТЕМНОЙ ЭНЗИМОТЕРАПИИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ТРОФИЧЕСКИХ ЯЗВ ВЕНОЗНОГО ГЕНЕЗА

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Современная стратегия и тактика лечения венозных трофических язв (ВТЯ) предполагают дифференцированный подход и комбинацию консервативных и хирургических методов. В работе представлены результаты исследования эффективности системной энзимотерапии (препарат «Флогэнзим», Mucos Pharma, Германия) у пациентов с варикозным расширением вен нижних конечностей клинического класса С6 с ВТЯ в I–III стадии раневого процесса. В исследовании участвовали 38 пациентов в возрасте от 12 до 82 лет. Они были разделены на основную (n = 20) и контрольную (n = 18) группы. Лечение длилось 1 мес. Использовали раневые повязки линейки Silcofix Professional (Pharmaplast, Египет), также все пациенты принимали «Детралекс» (Les Laboratoires Servier, Франция) и носили гольфы 2–3 степени компрессии. В основной группе в протокол лечения включили «Флогэнзим»: курс 30 дней, по 3 таблетки 3 раза в день. В результате полная эпителизация язвы на 3 неделе лечения была отмечена у 8 (40 %) пациентов, к концу лечения — у 18 (90 %), тогда как в контрольной группе — у 4 (22 %) и 9 (50 %) соответственно. У пациентов контрольной группы регенеративные процессы в области язвенного дефекта были слабо выражены по сравнению с основной группой. Иммунологический анализ показал существенное снижение содержания $CD4^+CD25^{Bright}$-клеток и повышение содержания Т-лимфоцитов с фенотипом $CD4^+CD45RO^+$ в основной группе, что соответствовало наблюдаемым положительным изменениям в клинической картине. Включение в протокол лечения иммуномодулирующего препарата «Флогэнзим» способствовало более быстрому регрессу клинических симптомов хронической венозной недостаточности и ускорению регенерации ВТЯ в I–III стадии раневого процесса.

Ключевые слова: варикозное расширение вен нижних конечностей, венозная трофическая язва, адаптивный иммунитет, субпопуляция лимфоцитов

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Varicose veins of lower extremities (VV) are one of the most common pathologic conditions of the peripheral vessels of lower extremities leading to the development of venous trophic ulcers (VTU) in some cases [1, 2]. VTU of lower extremities are a serious problem in modern medicine: in 10 % of cases VTU are persistent and non-responsive to conservative therapy [3]. Relapse rates remain high and range from 4.8 to 31.6 % after surgery and from 15.0 to 100.0 % after complex conservative treatment [4]. It is clear that attempts to influence individual components involved in the pathogenesis of the disease are not effective.

Recent studies show that in the treatment of venous ulcers, elimination of venous hypertension and valvular incompetence seen as the main causes of chronic venous insufficiency (CVI) [5–7] does not provide a desired effect. It is necessary to treat microcirculatory disorders that lead to chronic inflammation in the ulcer, constant leukocyte infiltration and changes in the metabolism of endothelial cells [8]. A characteristic feature of chronic inflammation is an imbalance between the humoral and cell-mediated immunity; however, only limited data are currently available on the role of immune disorders in the pathogenesis of VV [9, 10]. The few and rather contradictory results of the studies of the immune status of patients with VTU indicate that the severity of trophic disorders depends not only on the anatomical characteristics of the vein, but also on the inadequate response of immune cells, which is a chronic damaging factor [11–14].

One of the understudied methods of VTU treatment is systemic enzyme therapy (SET). Several studies have shown its efficacy, in particular when using Wobenzym (Mucos Pharma, Germany) for the treatment of CVI of various etiology (post-thrombotic syndrome disease and varicose vein disease) [15, 16]. The aim of this study was to evaluate the efficacy of conservative therapy supported with systemic enzymes (Phlogenzym by Mucos Pharma).

METHODS

The study included 38 patients with VV (C6) who received treatment for 1 month. The inclusion criteria were stage I-III recurrent VTU with the area of the ulcerous defect up to 30 cm^2, and patients' age from 18 to 82 years. The exclusion criteria were the presence of a concomitant pathology: type 1 and 2 diabetes, atherosclerosis of lower extremities, systemic vasculitis, rheumatoid arthritis, hormone and immune therapy.

The patients were divided into two groups. The control group received conservative treatment: wound dressings, compression and phlebotropic drug therapy. It included 18 patients (mean age of 60.1 ± 10.5 years) and consisted of 12 (66.7 %) women and 6 (33.3 %) men; 10 (55.6 %) patients were >60 years of age. The experimental group received conservative treatment and systemic enzyme therapy with Phlogenzym for 30 days, 3 tablets 3 times a day. It included 20 patients (mean age of 61.2±12.6 years) and consisted of 13 (65.0 %) women and 7 (35.0 %) men; 13 (65.0 %) patients were >60 years of age. Each group included 4 patients with stage III VTU and 3 patients with stage I VTU; the rest of the patients had stage II VTU.

In the course of treatment, wound dressings Silcofix Professional (Pharmaplast, Egypt) were used. In patients with stage I VTU, absorbent dressings (Fibrosorb, Fibroclean Ag) were used. Atraumatic povidone-iodine dressings (Silkofix POVI) were applied on the defect with persistent fibrin deposits after exudation has decreased. In patients with stage II-III VTU, hydrocolloid dressings with silver ions (Fibrocold Ag) were used. At the first sign of epithelialization, hypoadhesive mesh coatings with a lipidocolloid complex (Fibrotul, Fibrotul Ag) were used. All patients received Detralex (Les Laboratoires Servier, France) for 1 month and wore knee-high compression stockings (classes 2 and 3).

Fasting venous blood samples were taken for immunological analysis in the morning using Vacuette blood collection systems (Greiner Bio One, Germany). Lymphocyte surface receptors were evaluated by multiparameter immunofluorescent staining with monoclonal antibodies (IQ Products, the Netherlands). Before and after treatment, absolute and relative counts of lymphocytes in the peripheral blood with the following surface antigens were determined using laser flow cytometry (FACSCalibur platform, Becton Dickinson, USA) and Simulset and CellQuest software (BD Biosciences, USA): $CD19^+$, $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^+CD25^+$, $CD4^+CD25^{+Bright}$, $CD4^+CD45RA^+$, $CD4^+CD45RO^+$, CD45RA, CD45RO.

For the quantitative assessment of CVI symptoms ("heavy legs", pain, swelling, cramps) and the analysis of the wound healing dynamics (healing of the ulcer and the condition of the surrounding tissues), we used the Venous Clinical Severity Score (VCSS) and the ulcer and skin condition score. VCSS was used before and after treatment; ulcer assessment was performed before treatment and after 1 month of treatment. To assess the discomfort in daily activities, the Visual Analogue Scale (VAS) was used.

Bacteriological analysis of ulcer discharge was performed at the initial visit and after 2 weeks of treatment. The cultures were assessed using semiautomatic analyzers Sceptor and Crystal (Becton Dickinson).

Statistical analysis was performed using Statistica 6.0 software (StatSoft, USA). Statistical significance was determined using Student's t-test. The differences between mean values were considered statistically significant at $p < 0.05$. The data in the tables are presented as M ± m.

All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Pirogov Russian National Research Medical University in 2013.

RESULTS

Complete healing of ulcers in the control group was observed in 4 (22.2 %) patients after 3 weeks of treatment and in 9 (50.0 %) patients after 5 weeks. In the experimental group regeneration was much faster: complete epithelialization of the ulcer was observed in 8 (40.0 %) patients after 3 weeks of treatment and in 18 (90.0 %) patients by the end of treatment (Table 1). Healing was confirmed by the evaluation of such parameters as wound pain, hyperpigmentation, maceration, hyperemia and eczematous dermatitis. In the experimental group, we observed faster ulcer surface clearing of purulent and necrotic tissues, reduction of induration and hyperemia, more active formation of granulation tissue, and marginal epithelialization (Table 2). The patients of the experimental group also reported more significant pain relief and reduction of discomfort in the area of the ulcer in the course of treatment compared to the control group (Table 3).

Microbiological tests conducted before treatment identified the presence of *Staphylococcus aureus* in 40 % of patients and its microbial associations in 10 % of patients. After 2 weeks of treatment, only non-pathogenic and opportunistic microbes below the critical level of contamination were found in all patients.

In both groups, the analysis of cell subpopulations showed no significant changes in the absolute and relative counts of

Table 1. The results of treatment with and without Phlogenzym in patients with stage I–III venous trophic ulcers

Healing	Experimental group (n = 20)	Control group (n = 18)
Week 1	0	0
Week 2	0	0
Week 3	8 (40.0 %)	4 (22.2 %)
Week 4	7 (35.0 %)	2 (11.1 %)
Week 5	3 (15.0 %)	3 (16.7 %)

peripheral B-lymphocytes ($CD19^+$-cells), T-lymphocytes ($CD3^+$-cells) and major subpopulations of T-lymphocytes ($CD3^+CD4^+$- and $CD3^+CD8^+$-cells (Table 4).

The analysis of Treg-lymphocytes showed a significant decrease in the absolute and relative counts of $CD4^+CD25^{Bright}$ cells after treatment in patients who received Phlogenzym ($p < 0.05$) (Table 4). Conversely, in the control group increased levels $CD4^+CD25^{+Bright}$ cells were detected. Also, a significant increase in the relative count of peripheral $CD4^+CD45RA^+$ T-lymphocytes was seen in the control group, while the experimental group demonstrated an increase in peripheral $CD4^+CD45RO^+$ T-lymphocyte count.

The analysis of CD45-T-lymphocytes revealed almost no changes in $CD4^+CD45RA^+/CD4^+CD45RO^+$ and $CD45RA^+/CD45RO^+$ ratios after treatment in the control group, while the experimental group demonstrated a significant decrease in these parameters (Table 4).

DISCUSSION

The results of the lymphocyte subpopulation analysis and lymphocyte functional activity in patients with VV (C6) showed beneficial clinical effects of systemic enzyme therapy with

Table 2. Assessment of ulcers and surrounding tissues before treatment and after 1 week of treatment

Parameter	Experimental group (n = 20)		Control group (n = 18)	
	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment
Wound pain	**2.4 ± 2.1**	**1.3 ± 1.2***	**2.9 ± 1.9**	**2.4 ± 1.6***
Hyperpigmentation	1.0	1.0	1.0	1.0
Maceration	**0.4 ± 0.5**	**0.2 ± 0.3***	0.4 ± 0.5	0.3 ± 0.5
Hyperemia	**0.7 ± 0.5**	**0.2 ± 0.3***	**0.7 ± 0.5**	**0.4 ± 0.5***
Eczematous dermatitis	0	0	0	0

Note. The results are presented as M ± m. * — $p < 0.05$ when comparing two values within a group.

Table 3. Assessment of CVI symptoms severity and the degree of patient's discomfort before and after treatment

Parameter	Experimental group (n = 20)		Control group (n = 18)	
	Before treatment	After treatment	Before treatment	After treatment
Severity of clinical manifestations of CVI, the average score (VCSS scale)	5.6 ± 0.5	2.4 ± 0.7*	5.7 ± 0.5	3.9 ± 0.7*
The degree of patient's discomfort, the average score in cm (VAS scale)	4.9 ± 2.1	0.3 ± 0.8*	5.5 ± 1.1	1.2 ± 1.4*

Note. * — $p < 0.05$ when comparing two values within a group.

Table 4. Peripheral lymphocyte subpopulations in patients with VV (C6) who received treatment with and without Phlogenzym

Parameter		Experimental group (n = 20)		Control group (n = 18)	
		Before treatment	After treatment	Before treatment	After treatment
$CD19^+$	%	7.7 ± 0.79	8.8 ± 0.9	9.0 ± 0.9	10.2 ± 1.3
$CD3^+$		73.1 ± 1.76	74.6 ± 1.9	69.1 ± 1.7	72.9 ± 1.6
$CD3^+CD4^+$		47.0 ± 2.2	48.4 ± 2.2	44.3 ± 2.4	47.0 ± 1.9
$CD3^+CD8^+$		24.7 ± 2.8	23.9 ± 1.7	22.2 ± 1.7	24.8 ± 2.1
$CD3^+CD25^+$		4.1 ± 0.3	3.4 ± 0.3	7.6 ± 1.2	5.4 ± 0.4
$CD4^+CD25^{+Bright}$		**3.2 ± 0.3**	**2.4 ± 0.2***	**2.4 ± 0.3**	**3.5 ± 0.3***
$CD4^+CD45RA$		16.8 ± 2.0	16.3 ± 2.1	15.8 ± 1.7;	20.4 ± 2.0*
CD45RA		**57.4 ± 1.8**	**54.0 ± 1.8***	**53.3 ± 2.5;**	**63.0 ± 2.3***
$CD4^+CD45RO^+$		**26.7 ± 1.6**	**30.9 ± 1.5***	25.9 ± 1.4	28.4 ± 1.1
$CD45RO^+$		**36.5 ± 1.9**	**44.8 ± 2.2***	38.6 ± 2.5	41.6 ± 2.0
$CD4^+CD45RA^+/ CD4^+CD45RO^+$		**0.7 ± 0.1**	**0.5 ± 0.1***	0.6 ± 0.1	0.7 ± 0.1
$CD45RA^+/CD45RO^+$		**1.6 ± 0.1**	**1.3 ± 0.1***	1.4 ± 0.1	1.5 ± 0.1

Note. The results are presented as M ± m. * — $p < 0.05$ when comparing two values within a group.

Phlogenzym, a statistically significant reduction in the number of regulatory $CD4^+CD25^{+Bright}$ T-cells and an increase in $CD4^+CD45RO^+$ memory cells.

The described lymphocyte subpopulations are associated with the inhibition of the synthesis of proinflammatory cytokines and the antigen-presenting function of dendritic cells and macrophages, cell apoptosis induction, decreased generation of type 1 and 2 T-helpers (Th1, Th2) and reduced cytokine production by the latter. This leads to a less effective immune response and contributes to the development of chronic inflammation [17]. An important advantage of memory T-cells that constantly circulate in all organs and tissues of the body even in the absence of any inflammation over naive T-lymphocytes is their ability to detect antigens and eliminate them long before they reach secondary lymphoid structures [18].

After treatment completion, multidirectional dynamics of Treg and memory T-cells content in blood were revealed in the experimental group that corresponded with the observed positive clinical changes. This indicates a more effective immune response in patients who received Phlogenzym.

CONCLUSIONS

The present study demonstrated positive effects of systemic enzyme therapy on the regenerative processes in damaged tissues and on the function of T-cell mediated immunity in patients with VV (C6). The results of this study validate the inclusion of immunomodulatory drugs into the treatment protocol. Immunomodulatory drugs contribute to the regression of clinical symptoms of CVI and accelerate the healing process of stage I-III VTU.

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A COMPARISON OF GENDER DIFFERENCES IN CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS IN YOUNG ADULTS WITH MYOCARDIAL INFARCTION

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The article presents the analysis of clinical and angiographic characteristics and risk factors of myocardial infarction (MI) in men and women aged <45 years. The study included 35 patients with acute MI (15 females, 20 males) of the 14th Department of Cardiology, N. I. Pirogov City Clinical Hospital No. 1 (Moscow). The average age of female and male patients was 41.2 and 39.6 years, respectively. The majority of patients of both sexes had ST-elevation MI (STEMI) (88.6 %), among which Q-wave MI accounted for 60.0 % of cases and typical MI accounted for 71.4 % of cases. Sixty percent of patients of both sexes had no previous history of CHD. Almost all risk factors (dyslipidemia, hypertension, early family history etc.) were seen more often in women compared to men, except smoking which was found to be a risk factor in 55 % of men vs. 6 % of women (p <0.05). The coronary angiography data showed the prevalence of the right type of coronary circulation (70 % of patients) and single-vessel disease (80 %) with coronary stenosis of more than 75 %. The time to diagnosis was 2.1 times greater in women than in men accounting for an average of 9.2 and 4.3 hours, respectively. The main causes of delayed MI diagnosis before admission were late patient referral or diagnostic errors.

Keywords: myocardial infarction, young age, angiographic data, gender-specific characteristics, risk factor

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ГЕНДЕРНОЕ СРАВНЕНИЕ КЛИНИКО-АНГИОГРАФИЧЕСКИХ ОСОБЕННОСТЕЙ ИНФАРКТА МИОКАРДА У ПАЦИЕНТОВ МОЛОДОГО ВОЗРАСТА

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В статье представлены результаты исследования по определению клинико-ангиографических особенностей и факторов риска развития инфаркта миокарда (ИМ) у мужчин и женщин моложе 45 лет. В исследование включили 35 больных острым ИМ (15 женщин и 20 мужчин), пациентов 14-го кардиологического отделения Городской клинической больницы № 1 имени Н. И. Пирогова (Москва). Средний возраст женщин составил 41,2 года, мужчин — 39,6 года. В подавляющем большинстве случаев встречался ИМ с подъемом ST (88,6 %), Q-образующий (60,0 %), типичный вариант (71,4 %). У 60 % молодых пациентов обоих полов в анамнезе отсутствовали симптомы ИБС. Практически все изученные факторы риска (дислипидемия, артериальная гипертензия, ранний семейный анамнез и др.) были свойственны женщинам в большей степени, чем мужчинам. Исключение составило курение, которое являлось риском для 55 % мужчин и только для 6 % женщин (p <0,05). Данные коронароангиографии продемонстрировали превалирование правого типа коронарного кровоснабжения (70 % пациентов) и односсудистого поражения (80 %) с сужением коронарных сосудов более чем на 75 %. На верификацию диагноза ИМ у женщин тратили в 2,1 раза больше времени, чем у мужчин: в среднем 9,2 и 4,3 ч соответственно. Основными причинами поздней диагностики ИМ на догоспитальном этапе были несвоевременное обращение пациентов к врачу или неправильный диагноз.

Ключевые слова: инфаркт миокарда, молодой возраст, ангиографические данные, гендерные особенности, фактор риска

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Coronary heart disease (CHD), the lethal manifestation of which is myocardial infarction (MI), is one of the main causes of death in the developed countries [1]. It has been commonly considered as a disease of men, and the risk of its development in women has often been underestimated [2].

Male gender is a risk factor of CHD, especially in people under 45 years of age [3, 4]. Low incidence of CHD in women of this age is associated with a protective effect of the blood estrogen on the endothelium [5]. Numerous studies have shown that the decrease in estrogen in menopausal women is associated with the development of the endothelial dysfunction and lipid deposition in the vessel wall, which may eventually lead to atherosclerosis [6, 7]. Furthermore, the mortality rate after the first MI and surgical myocardial revascularization in women is higher than in men [8, 9]. It was found that 26 % of women and 19 % of men over 45 years of age die within a year after the first MI. Five-year mortality rates are 47 % and 36 %, respectively [10]. Complications, such as heart failure and stroke, are more likely to develop in women [10].

The pathogenesis of CHD in women is not fully understood; it is not always possible to timely diagnose and cure the disease [3]. High female mortality from MI may be associated

with the underestimation of the severity of coronary pathology and various risk factors as well as patients' negligence to their health. Numerous studies have shown that many women with acute coronary syndrome do not receive appropriate therapy [11–13], coronary stenting [11–14] or timely reperfusion [12, 13, 15–19].

Researchers are increasingly interested in the gender aspect of cardiovascular diseases in young adults, as their early diagnosis and treatment have a significant social and economic impact. Nevertheless, the data on the characteristics of the CHD pathogenesis in young women are still scarce [3]. The present study is aimed to determine the clinical and angiographic characteristics and risk factors of myocardial infarction in men and women under 45 years of age.

METHODS

The study included 35 patients with acute MI (15 females, 20 males) of the 14th Department of Cardiology, N. I. Pirogov City Clinical Hospital No. 1 (Moscow). The average age of female and male patients was 41.2 and 39.6 years, respectively. The inclusion criteria were age <45 years and the presence of myocardial infarction (in accordance with the diagnostic criteria described in [20]). Exclusion criteria were age >45 years, concomitant cardiovascular pathology, and severe pathology of the liver and kidneys. All patients gave informed consent.

We have analyzed the patients' data obtained through questionnaires and the results of a standard clinical check-up that included anthropometric measurements, body mass index (BMI) calculation, history taking, health assessment at the time of our study (reduced tolerance to physical exercise during a treadmill test), assessment of the risk factors (smoking, alcohol consumption, eating habits, family history, hypertension, diabetes, lipid profile and intake of oral contraceptives). The results of the following laboratory and instrumental tests were also used:

– lipid profile (cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triacylglycerols and atherogenic index);

– cardiotests (measuring the levels of creatine kinase-MB, troponin and myoglobin);

– blood coagulation profile (international normalised ratio, activated partial thromboplastin time, prothrombin index and fibrinogen);

– chest X-ray;

– electrocardiogram (12 standard leads at rest);

– transthoracic echocardiography using the Aplio MX ultrasound scanner (Toshiba, Japan); to assess left ventricular hypertrophy and systolic and diastolic dysfunctions, the end-systolic and end-diastolic volumes and left ventricular ejection fraction were measured;

– coronary angiography using the Infinix VC-i (Toshiba) angiography system (the procedure was performed on 12 women and 18 men).

Data were statistically processed using BioStat 2009 5.8.3.0 (AnalystSoft, USA) software. To determine the significance of differences ($p < 0.05$), Student's t-test was applied.

RESULTS

The majority of patients (88.6 %) had ST-elevation MI (STEMI), among which Q-wave MI accounted for 60.0 % of cases and typical MI accounted for 71.4 % of cases (Table 1). Forty percent of patients of both sexes had no previous history of CHD (angina pectoris or previously diagnosed CHD). The average time to MI diagnosis in women was 2.1 times greater than in men ($p < 0.05$) accounting for an average of 9.2 h. The main causes of delayed MI diagnosis before admission were late patient referral or diagnostic errors.

Analysis of key cardiovascular risk factors has shown that all of them, except smoking, are more typical in women (Table 2, Fig. 1). Only 7 % of the patients had no risk factors, whereas 1 out of 3 women had a combination of two factors; over 50 % of women had a combination of three risk factors.

Assessment of the coronary bed characteristics based on the coronary angiography data revealed that 70.0 % of patients had the right type of coronary circulation and single-vessel disease (80.0 %) with >75.0 % coronary stenosis (Table 3, Fig. 2). Interestingly, no patient in the female group had multivessel disease, which confirms the literature data on the rarity of this form of disease in younger adults [20]. Lesions were most commonly found in the anterior interventricular artery (in 4 women and 5 men) and right coronary artery (in 3 women and 7 men). Only one woman and two men had a normal angiogram, in other cases atherosclerotic coronary stenosis of varying degrees was found (Fig. 2).

The diastolic dysfunction was found to be the most frequent MI complication in both groups observed in 55.0 % of men and 60.0 % of women (Fig. 3). The systolic dysfunction was less common: it was found in 45.0 % of men and 20.0 % of women. The left ventricular aneurysm and arrhythmias were found only in the female group.

DISCUSSION

Dyslipidemia was the most common risk factor in our study, both in men and women, which correlates with the data from international studies involving young patients [3]. It was shown that blood cholesterol levels directly correlated with the CHD

Table 1. Characteristics of myocardial infarction (MI) in young adults (<45 years) (* — $p < 0.05$)

Parameter	Women (n = 15)	Men (n = 20)	Total (n = 35)
Average time to diagnosis. h	**9.2 ± 2.4**	**4.3 ± 2.1***	6.5 ± 4.5
MI without ST-elevation	4 (26.7 %)	0	4 (11.4 %)
MI with ST-elevation	11 (73.3 %)	20 (100.0 %)	31 (88.6 %)
Q (+)	7 (46.7 %)	14 (70.0 %)	21 (60.0 %)
Q (–)	8 (53.3 %)	6 (30.0 %)	14 (40.0 %)
Typical MI	10 (66.7 %)	15 (75.0 %)	25 (71.4 %)
Atypical MI	5 (33.3 %)	5 (25.0 %)	10 (28.6 %)
MI complications	10 (66.7 %)	12 (60.0 %)	22 (62.8 %)
History of CHD	6 (40.0 %)	8 (40.0 %)	14 (40.0 %)

Table 2. Quantitative characteristics of some of the risk factors of cardiovascular disease in young adults (<45 years) with myocardial infarction (* — p <0.05)

Parameter	Women (n = 15)	Men (n = 20)
Systolic blood pressure, mmHg	**163.0 ± 29.9**	**176.0 ± 27.4***
Diastolic blood pressure, mmHg	88.0 ± 13.2	98.0 ± 19.7
Body mass index, kg/m^2	33.0 ± 6.1	32.0 ± 6.1
Waist circumference, cm	**102.0 ± 24.7**	**111.2 ± 8.9***
Smoking index (pack-years)	**2.2 ± 6.1**	**14.2 ± 15.2***
Cholesterol, mmol/l	5.0 ± 1.1	5.2 ± 1.3
Triacylglycerols, mmol/l	1.6 ± 0.3	1.6 ± 0.4
HDL, mmol/l	1.5 ± 0.4	1.7 ± 1.7
LDL, mmol/l	2.3 ± 0.2	2.4 ± 1.1

Fig. 1. The prevalence of key risk factors in young adults (<45 years) with myocardial infarction. The proportion of patients with at least one risk factor is shown, % (* — p <0.05)

risk. Blood cholesterol level above 6.76 mmol/l indicated a risk of developing CHD and a 4–5 fold risk of MI compared to the individuals with normal cholesterol levels [2].

It is known that arterial hypertension, which is a risk factor for CHD, is more common in women over 65 than in men of the same age [1]. Hypertension was the second most common risk factor in our study, and despite the small study population, we discovered the same tendency in younger adults (<45 years): 80 % of women and 50 % of men were susceptible to high blood pressure (Fig. 1). The risk of death from CHD in women with hypertension was 10 times higher than in young women without hypertension, and 1.5 times higher than in men [1]. The data collected by the American Heart Association (AHA) confirm that hypertension is one of the major risk factors of MI in women, population attributable risk here being 36 %, which indicates a possibility of reducing MI incidence by 36 % on eliminating the risk factor [8].

We have also found that women had a family history of early CHD and MI more often than men (73 % and 60 %, respectively). The international literature emphasises the importance of this factor for younger patients [3, 21], especially males [22].

Almost half of our female patients were overweight, one-third were obese. According to the Framingham Heart Study, the risk of CHD in obese women is 2 times higher than in women with normal body weight [23]. This conclusion was confirmed by the Nurses' Health Study [1, 24].

In the developed countries, smoking is one of the most common risk factors for CHD among people of both sexes under 45 years of age [1]. Young women are especially sensitive to the effects of nicotine [25] and young adults make up a greater proportion of smokers [22]. According to the studies from China and other countries, 70 to 90 % of young patients with acute myocardial infarction are smokers [3, 26, 27]. Young patients with ST-elevation MI are also more likely to smoke than older patients [3].

It is generally known that diabetes mellitus [DM] significantly increases the risk of CHD and IM [1]. In our study diabetes was found in every third woman and every fourth man. It was shown that the risk of MI associated with the metabolic syndrome is significantly higher in young women than in elderly women [28]. Furthermore, DM is associated with a higher risk of cardiovascular disease in women compared to men [29, 30].

In our study, the equal proportions (60 %) of men and women under 45 years of age had MI as the first clinical manifestation of CHD. The typical form of MI was diagnosed in 75 % of men and 67 % of women, while the incidence of atypical forms was slightly higher in women. This is consistent with the data obtained by other researchers [31-33]. We also found that in younger women coronary stenosis was less frequent and less severe than in young men. The same tendency was observed by Lebedeva et al. [2]. According to the AHA, the gender aspect of clinical manifestations affects the quality of CHD diagnosis and management of patients: women are often misdiagnosed, their myocardial revascularization is delayed,

Table 3. Coronary angiography in young adults with myocardial infarction

Parameter	Women (n = 12)	Men (n = 18)	Total (n = 30)
Left type of coronary circulation	1 (8.3 %)	5 (27.7 %)	6 (30.0 %)
Right type of coronary circulation	8 (66.7 %)	13 (72.3 %)	21 (70.0 %)
Balanced type	3 (25.0 %)	0	3 (10.0 %)
Single-vessel disease	10 (83.3 %)	14 (77.7 %)	24 (80.0 %)
Two-vessel disease	2 (16.7 %)	1 (5.6 %)	3 (10.0 %)
Multivessel disease	0	3 (16.7 %)	3 (10.0 %)
Intact vessels	1 (9.1 %)	2 (10.0 %)	3 (10.0 %)

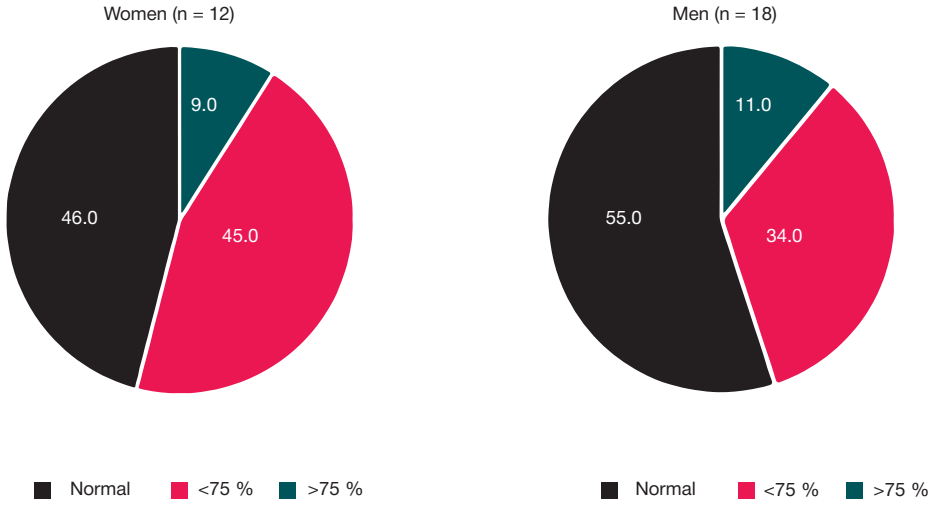

Fig. 2. The distribution of patients within the group by the degree of the coronary artery constriction, %

Fig. 3. The incidence of myocardial infarction complications in young adults (<45 years). The proportion of patients with at least one complication type is shown, %

and mortality caused by MI among them is increasing [2, 8].

A number of studies have shown that women with MI receive therapy later than men [34-37]. Kaur et al. [37] reported that the average time elapsed from the onset of MI symptoms to the moment the patient finally visited the doctor was 53.7 and 15.6 h for women and men, respectively. Our data were different: 9.2 ± 2.4 and 4.3 ± 2.1 h, respectively ($p < 0.05$).

CONCLUSIONS

MI was the first clinical symptom of the coronary heart disease in 60 % of cases in men and women under 45 years of age. Women started to seek medical advice 2.1 times later than men. This indicates a lack of suspicion among doctors and awareness among female patients concerning the risk of MI, especially in young women. Men and women were typically diagnosed with ST-elevation MI, Q-wave MI and typical MI; however, atypical MI was more often seen in women. The most common risk factors for MI were dyslipidemia, hypertension, family history of CHD and overweight. Our analysis showed that young women were at greater risk of CHD than young men.

The causes of early atherogenesis in young women require further research. Raising awareness of MI symptoms among young women is also highly important.

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TREATMENT AND REHABILITATION OF CHILDREN WITH ELECTROTHERMAL INJURY

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Electrothermal lesions are most often seen in pediatric injuries. This type of injury is uncommon, but is one of the leading causes of death and disability in children. Using medical records, we analyzed the outcomes of the treatment and rehabilitation of children with electrothermal lesions (n = 51) admitted to Pediatric Burn Center, Children's City Clinical Hospital No. 9 (Yekaterinburg, Russia) over the period from 2010 to 2015. The patients were divided into two groups: Group 1 (39 children) had injuries from electrical household appliances and Group 2 (12 children) sustained high-voltage injuries. Primary surgical debridement was performed on all children; the extent and depth of the burns were established. The next step of surgical treatment for Group 1 included necrectomy and single-stage dermatoplasty; in Group 2 necrectomy and the first stage of skin grafting (formation of a skin flap) were performed. Subsequently, all patients in Group 2 received skin grafts for final closure of the skin defect. The duration of treatment in Group 2 was 2 times longer than in Group 1, due to larger burn areas (an average of 12 % vs. >5 %), longer burn shock (>24 h vs. 10 h), higher complication rate, and multiple stages of surgical treatment. Six patients from Group 2 received surgical amputation. However, the division into groups according to the physical properties of the electric current can be beneficial for the development of more effective treatment algorithms.

Keywords: electrical current, electrothermal lesion, electrical injury, combustiology, children, pediatric injuries

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ОСОБЕННОСТИ ЛЕЧЕНИЯ И РЕАБИЛИТАЦИИ ДЕТЕЙ С ЭЛЕКТРОТЕРМИЧЕСКОЙ ТРАВМОЙ

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Электротермические поражения характерны для детского травматизма. Этот вид травмы встречается редко, но занимает одно из первых мест в структуре причин летальных исходов и инвалидности у детей. В статье по историям болезни проанализированы результаты лечения и реабилитации детей с электротермическими поражениями (n = 51), находившихся в 2010–2015 гг. на лечении в Детском ожоговом центре Детской городской клинической больницы № 9 (Екатеринбург). Сформировали две группы: в первой 39 детей получили травмы при контакте с бытовыми электроприборами, во второй 12 детей пострадали от высоковольтного тока. Первичную хирургическую обработку проводили всем детям, устанавливали степень и глубину ожогов. На следующем этапе в первой группе проводили некрэктомию и одноэтапную пластику, а во второй — некрэктомию и первый этап пластики (формирование лоскута). В последующем во второй группе выполняли второй этап пластики кожными лоскутами разных видов для окончательного закрытия дефекта кожи. Выяснили, что продолжительность лечения детей во второй группе была в 2 раза больше, чем в первой, вследствие большей площади ожогов (в среднем 12 % против менее 5 % в первой группе), большей продолжительности ожогового шока (более 24 ч по сравнению с 10 ч в среднем в первой группе), развитием осложнений, многоэтапностью лечения. Во второй группе у 6 пациентов применили ампутацию. Тем не менее лечение детей с разделением на группы с учетом физических характеристик тока перспективно для создания более эффективных алгоритмов помощи.

Ключевые слова: электрический ток, электротермическое поражение, электротравма, комбустиология, дети, детский травматизм

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Electrothermal injury is considered a specific burn injury type because of the nature of the damaging factor, the electric current. It causes both local and systemic injury. The type of pediatric electrothermal injury depends on the age and social activity of the child. Young children are more likely to be injured by electrical household appliances, whereas teenagers are more likely to sustain high-voltage shock.

It is not possible to assess the total or regional incidence of electrothermal injury in children, since a large number of patients do not seek medical attention, and in rare cases death occurs at the scene of an accident before first aid can be provided [1–3]. In the overall structure of hospital admissions, electrothermal injuries account for 1–8 %, according to the data from a number of burn centers [4].

Children admitted to a hospital after sustaining an electrothermal injury need surgical treatment aimed at restoring skin integrity and eliminating functional disorders. Due to a low incidence of electrothermal injuries and the severity of the sequelae, the physicians should be particularly careful when dealing with young patients and strictly adhere to the algorithms of medical treatment considering the dependence of the severity of a patient's condition on the physical characteristics of the electric current [4–5]. Typical of this type of burns are deep and spreading lesions of subcutaneous tissue, neurovascular structures or muscles, through which the electric current travels faster than through the skin surface, as resistance in these body areas is different [6–8].

Current literature, both Russian and international, does not provide sufficient data on how the characteristics of the electric current influence treatment decisions. There are single case reports, descriptions of shock treatment principles, intensive care and skin repair techniques. But there is no standardized approach to the management of patients who sustained injuries from different types of electric current [9–11]. The aim of this study was statistical analysis of the treatment and rehabilitation outcomes in children with different electrothermal injuries admitted to the Pediatric Burn Center, Pediatric City Clinical Hospital No. 9 (Yekaterinburg).

METHODS

We performed a retrospective analysis of medical records of children with electrical injury treated in the Pediatric Burn Center over the period of 2010–2015. The study included 51 children (39 boys, 12 girls). About half of the children were 3-years old or younger (24 patients), 10 patients were 13–15 years old (adolescents), 9 patients were 8–12 years old (primary school age), 8 patients were 4–7 years old (preschool children). The patients were divided into two groups according to the source of the electric current: group 1 included 39 (76 %) children with electrothermal lesions from electrical household appliances; group 2 included 12 (24 %) children with high-voltage shock.

The choice of surgical treatment depended on the characteristics of the electric current. Primary surgical debridement was performed in all children; the extent and depth of the burns were established. The next step was different for both groups: necrectomy and single-stage dermatoplasty was performed in group 1, while necrectomy and the first stage of skin grafting with the formation of a skin flap were performed in group 2. Subsequently, the patients from group 2 underwent the second stage of dermatoplasty with various skin grafts for final closure of the skin defect. Enzyme therapy and scar dermatoplasty were also performed for better cosmetic effect in group 2.

The localization of lesions, burn areas, burn shock duration, overall treatment time, and the level of disability were evaluated.

RESULTS

The incidence of electrothermal injuries in the Pediatric Burn Center, Children's City Clinical Hospital No. 9, was <5 % of the total number of children admitted to the Center over the period of 2010–2015. No deaths were observed. The results of treatment and rehabilitation of patients are shown in table. In group 1, an electrical injury of a hand with limited area grade IIIB–IV burns was most often seen at the site of direct contact with the current, and the lesion area was less than 5 %. The duration of burn shock was less than 24 h (10 h in average). In group 2, burn location was different and involved the head, neck, back, and upper limbs; burn areas were larger (from 5 to 15 %, an average of 12 %), burn shock was longer (over 24 h) and neurological symptoms were observed.

The children from group 1 were closely monitored until the formation of the demarcation line. This allowed for sparing surgical debridement followed by skin grafting. In group 2, aggressive surgical treatment was chosen to rescue the damaged segment of the body. Here, treatment duration was 2 times longer compared to group 1. The disability rate in

Results of treatment and rehabilitation of children with electrothermal lesions based on the characteristics of the electric current

Parameter	Group 1 (n = 39)	Group 2 (n = 12)
Current characteristics	220 B / 5 A	>1000 B / 100 A
Burn area	<5 % of the body	5–15 % of the body
Burn grade	II–IIIA. (n = 14) IIIB–IV. (n = 25)	IIIB–IV. (n = 12)
Duration of burn shock	Less than 24 h, not always manifested	More than 24 h
Combined injury	–	12 cases
Treatment	1) Primary surgical revision 2) Debridement 3) Single-staged skin grafting 4) Dressings	1) Primary surgical revision 2) Debridement (primary and secondary), including amputation 3) Multi-staged skin grafting 4) Dressings 5) Rehabilitation
Number of cases of disability	–	6 cases
Time of treatment, bed-days	3–34	9–75

group 2 was 50 %. In 6 cases, amputation was performed due to inability to preserve the integrity of tissues. Also, in group 2 patients, heart pathology (ectopics), neurological disorders (paresthesia, paresis, and other disorders of the peripheral innervation) were observed. These children were referred to cardiologists and neurologists in a primary care facility for further rehabilitation.

Electrothermal injuries were most common in children under the age of 3. In all studied cases, they were caused by home appliances and resulted from the lack of parental control. The second largest group with regard to the incidence of injuries was constituted by adolescents with high-voltage injuries resulting from the lack of age-appropriate activities during leisure time: children were unsupervised by adults. Eighty three percent of children resided not in Yekaterinburg but in other populated areas of the Sverdlovsk region.

DISCUSSION

Treatment and rehabilitation of children with high-voltage electrothermal lesions required more time, which was due to the combined nature of the injuries, a larger burn area, prolonged burn shock, disorders of the cardiovascular, nervous and respiratory systems, and multi-staged treatment in both in-patient and out-patient care facilities. Distributing patients into groups allowed us to develop algorithms of care based on the characteristics of the electric current and the severity of injury that directly influenced the strategy of surgical treatment and rehabilitation. Aggressive surgical intervention at an early stage provided for maximum possible preservation of damaged tissues. Methods proposed previously did not include early skin grafting [12–14].

Interestingly, we observed a decreased incidence of household electric injuries in preschool children; we also registered high-voltage injuries in this group of patients for the first time. The same tendency was observed in primary school children. In general, over the past 6 years there has been a decrease in the incidence of electric injuries in both age groups, while from 2014 to 2015 no cases of high-voltage injuries were registered. Apparently, it is the result of the public campaign in the media and in schools to properly handle electrical appliances. Inspections of industrial enterprises and railroads aimed at timely prevention of injuries in children also had their effect.

CONCLUSIONS

The prognosis of organ preservation in electrothermal injuries depends on the physical characteristics of the electric current, the location of burns, and the degree of trophical and neurological disorders in the affected area. The treatment of high-voltage injuries with the burn area of >5% should include early surgical debridement and skin grafting (formation of a skin flap), followed by close wound monitoring, and, if necessary, extension of the debridement area and different types of dermatoplasty.

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THE HYPOTHESIS OF TISSUE-SPECIFIC ACTION OF DIPHTHERIA TOXIN

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Diphtheria is an infection caused by toxigenic strains of *Corynebacterium diphtheriae*. The pathogen releases the toxin that affects heart, kidneys, adrenal gland, as well as spinal and cerebral nerves. Tissue- and organ-specific action of diphtheria toxin is considered to be associated with the blood supply to these organs. We propose the hypothesis that takes into account the physical and chemical properties of the toxin molecule (positively charged R-domain in the B subunit) and cell expression of different types of the HB-EGF receptor and CD9 co-receptor, which are responsible for the toxin penetration into the cell. The proposed hypothesis explains the possible mechanisms of diphtheria complications.

Keywords: diphtheria, diphtheria toxin, *Corynebacterium diphtheriae*, HB-EGF receptor, CD9 co-receptor, tissue specificity, organ specificity.

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ГИПОТЕЗА ТКАНЕСПЕЦИФИЧНОСТИ ДЕЙСТВИЯ ДИФТЕРИЙНОГО ТОКСИНА

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Дифтерия — инфекция, вызываемая токсигенными штаммами бактерии *Corynebacterium diphtheriae*. Возбудитель выделяет токсин, который воздействует на сердце, почки, надпочечники, спинномозговые и черепно-мозговые нервы. Ткане- и органоспецифичность действия дифтерийного токсина принято связывать с особенностями кровоснабжения указанных органов, однако в статье предложена гипотеза, учитывающая физико-химические свойства молекулы токсина (наличие положительно заряженного R-домена в субъединице B молекулы) и представленность в клетках различного типа рецептора HB-EGF и корецептора CD9, с которыми токсин связывается для проникновения в клетку. Дано объяснение возможных механизмов осложнений при дифтерии с учетом гипотезы.

Ключевые слова: дифтерия, дифтерийный токсин, *Corynebacterium diphtheriae*, рецептор HB-EGF, корецептор CD9, тканеспецифичность, органоспецифичность

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Diphtheria is a classic toxemic infection caused by *Corynebacterium diphtheriae*, a gram-positive bacterium, and most importantly by its toxin. The pathogen penetrates the mucous membranes of the oropharynx, nasopharynx, larynx and trachea and sometimes those of eyes and genitals. A local inflammatory focus is formed accompanied by necrotic cell death, blood plasma coagulation, edema, and formation of a whitish-gray coating over the mucosal surface. In the multilayer epithelium of the nasopharynx, epiglottis and vocal cords, the membrane is inseparable from the underlying tissue, while in the monolayer epithelium of the larynx, trachea and bronchi the membrane is easily separated and may cause airway obstruction and asphyxia.

The toxin secreted by toxigenic strains of *C. diphtheriae* enters the bloodstream and selectively affects the heart, kidneys, adrenal glands, and spinal and cranial nerves [1]. In this paper, we present the hypothesis that the tissue and organ specificity of the toxin can be explained by both physical and chemical properties of the molecule as well as by the structure of the cell membranes of the target organs.

Structure of the toxin and its penetration into the cell

Diphtheria toxin (DT) is a protein with a molecular weight of 58 kDa (535 amino acid residues, isoelectric point, pI, of 5.9). It consists of two subunits (A and B); the a subunit exhibits nuclease activity [2] and ADP-ribosyltransferase activity towards elongation factor EF-2. It blocks the cellular mechanism of protein synthesis, which results in cell apoptosis. The B subunit consists of the transmembrane (T) domain and the receptor binding (R) domain responsible for binding to HB-EGF [3].

The a subunit of the toxin is delivered into the cell in several steps (Fig. 1). In the first step (pH of 7.4, DT electrical charge of –9.44), the R domain of the B subunit mediates the binding of the toxin to its receptor HB-EGF and co-receptor CD9 [3]. In the second step, clathrin-dependent endocytosis of the toxin occurs; the clathrin-coated vesicles containing DT are shortly transformed into early endosomal vesicles. While PIP phosphatase and the heat shock protein Hsp70 separate the primary clathrin coat from the vesicles [4], and new components (COPI proteins, Arf, Rab, etc.) begin to

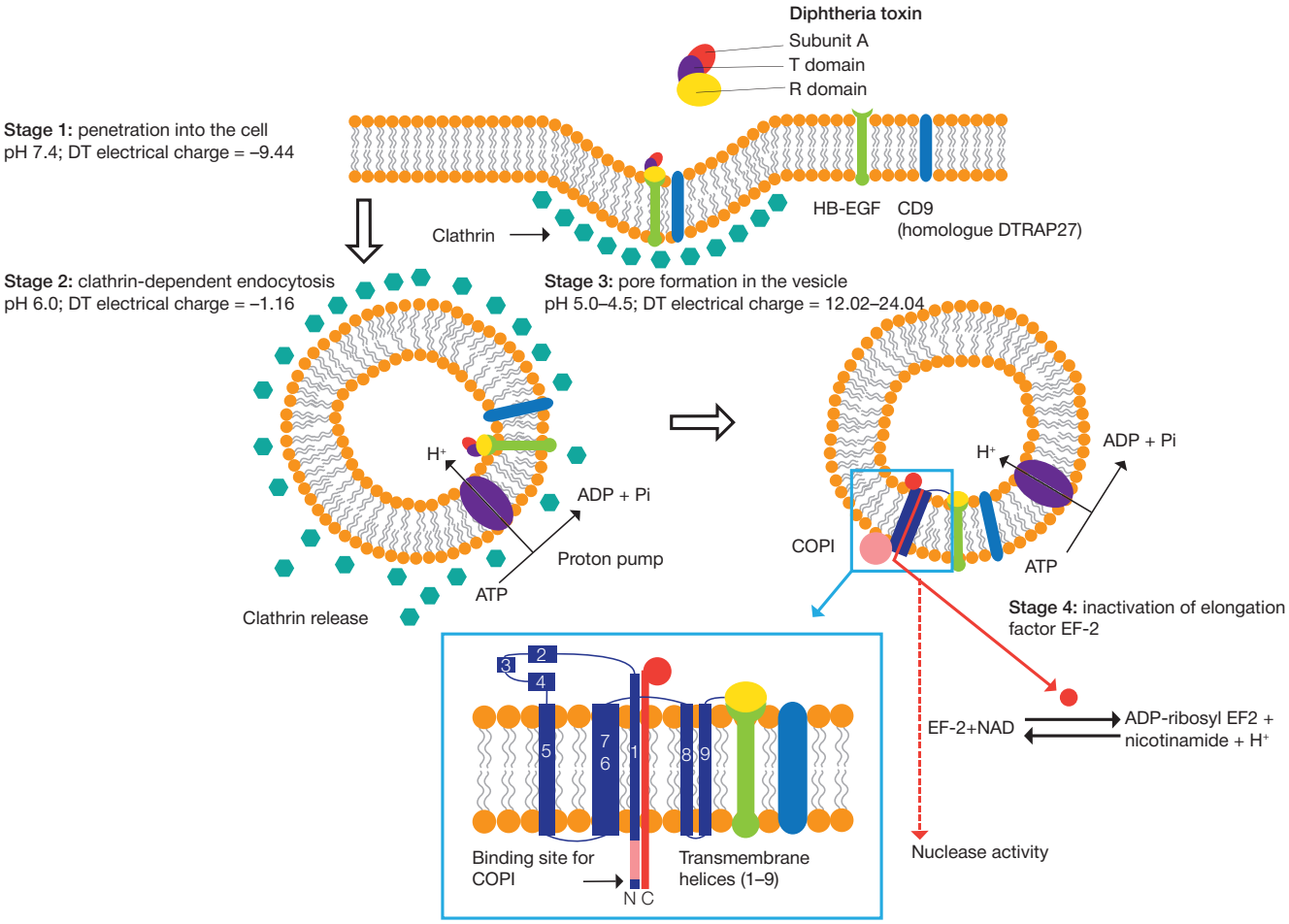

Fig. 1. The mechanism of toxin penetration into the cell

adhere to it [3, 4], the proton pump acidifies the medium inside the vesicle, thus lowering the pH to 6.0 [4] and changing the electrical charge of DP to −1.16. In the third step, the pH within the vesicle drops to 5.0–4.5 [4], and the protein charge becomes positive (from 12.02 to 24.04). These conditions are necessary to modify the conformation of the T domain of the toxin B subunit and to form a pore in the vesicle. The T domain consists of 9 transmembrane helices (TH), which in turn are packed into three layers: the first comprises amphiphilic TH1–TH3, the second comprises hydrophobic TH5–TH7, and the third comprises TH8 and TH9 forming the central core [3]. TH1 closely interacts with the catalytic subunit and also has sites for binding to COPI complex, which plays a crucial role in the A subunit translocation (along with TH2–TH4). In the fourth stage, a free subunit inactivates elongation factor EF-2.

Tissue and organ specificity of the toxin

The tissue specificity of the toxin can be explained by its physical and chemical properties, namely, the presence of the R domain (amino acid residues 432–535 [3]) that ensures the interaction between the toxin and HB-EGF. The positive charge of this domain (8.2 at pH of 7.4, pI of 10.43) determines the ability of the toxin to bind to a negatively charged membrane receptor. If a cell membrane can be imagined as an equivalent to an electrical circuit, then it has both capacitive (C) and resistive properties (R) defined by the components of the membrane itself (phospholipids and proteins). One side of the membrane is charged positively and the other is charged negatively [5]. A deficit of cations on the inner membrane creates a negative charge inside the cell, while their excess on the outer membrane surface creates a positive charge on the outside. Na^+/K^+ ATPase serves as a kind of battery (E) establishing a voltage difference by pumping $3Na^+$ out and $2K^+$ into the cell. Such are the passive electrical properties of the membranes [5]. In turn, the excitable cells are able to redistribute ions during depolarization. This phenomenon is the basis of our hypothesis explaining the tissue specificity of the toxin. The excess of cations outside the membrane that generates the resting potential repels DT, and temporary ion redistribution during the action potential attracts it. There are also specific lipids: gangliosides that impart special properties to highly specialized cells, such as neurons and cardiomyocytes. In these cells, gangliosides may account for 5–10 % of the total lipids [4]. Sialic acids present in the molecular structure of gangliosides generate a strong negative charge, which determines their tropism towards positively charged molecules.

In the modern literature, organ specificity of DT has been linked to the peculiarities of the blood supply to the targeted organs [1]. However, neither liver nor the gastrointestinal tract are affected by the toxin, even though they receive up to 25 and 10 % of the cardiac output, respectively. Here, the assumption is that the organ specificity of the toxin can be attributed to the presence of HB-EGF and CD9 and their ratio in different cell types. According to RefExA database [6], HB-EGF is present in large amounts in the spinal nerves (Spinal_c), thyroid cells (Thyroid), pulmonary epithelium (Lung), smooth muscle tissue (Sm_mscl), cardiomyocytes (Heart), renal epithelium

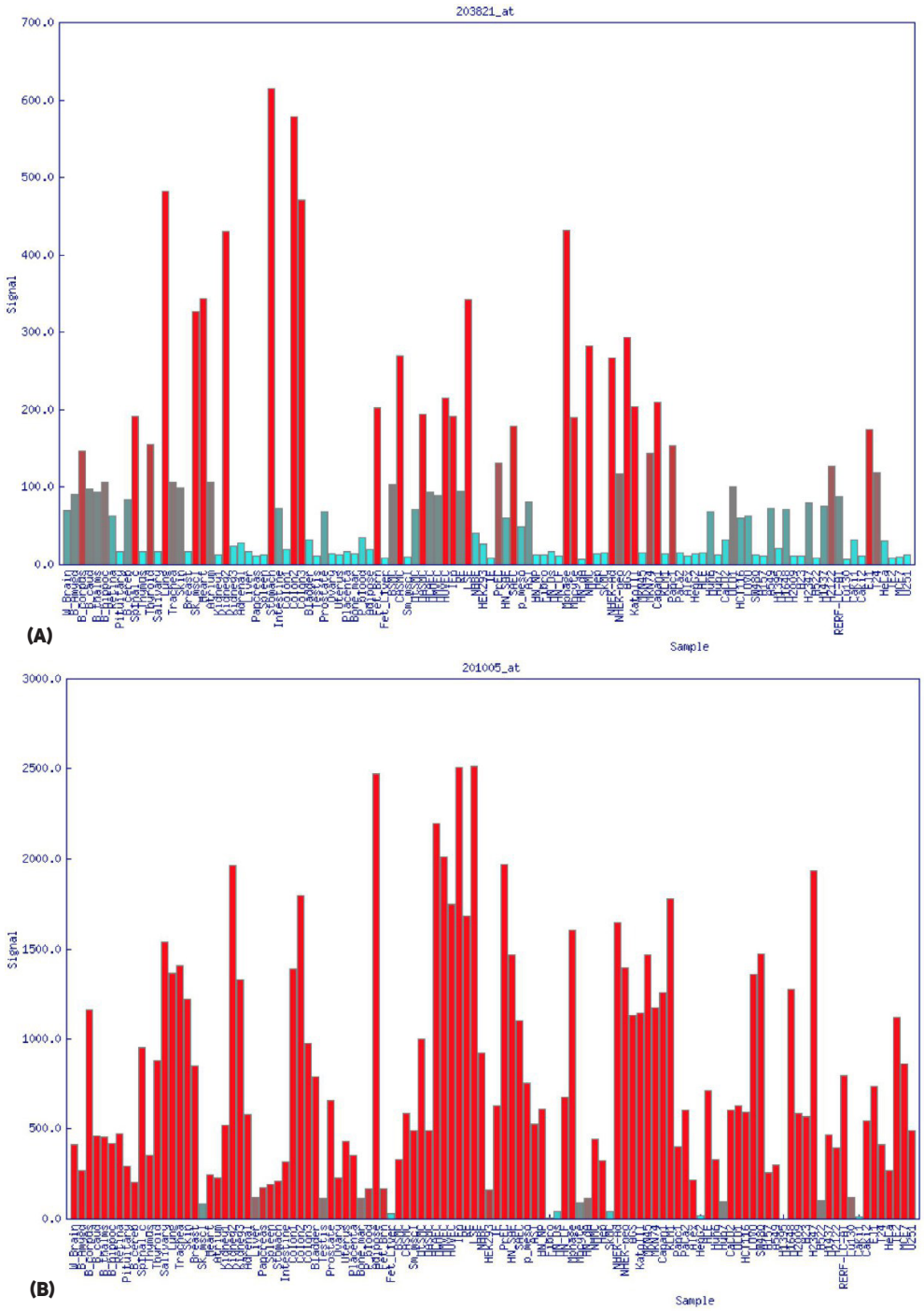

Fig. 2. Expression of the HB-EGF **(A)** and CD9 **(B)** in human tissues (according to RefExA database [6])

(Kidney_2), stomach epithelium (Stomach), and intestinal epithelium (Colon2, Colon3) (Fig. 2A). The concentration of the co-receptor CD9 is high in most cell types, except for the skeletal myosymplasts (Sk_mscl), liver cells (Liver), spermatogenic epithelium (Testis), and hematopoietic bone marrow cells (Bone_mar) (Fig. 2B). To have any effect, the diphtheria toxin requires both HB-EGF and CD9, a criterion which is met by the cells of the heart, lungs, gastrointestinal tract, kidneys, thyroid gland, spinal and cerebral nerves.

Complications of diphtheria in the light of the hypothesis

The first complication of the hypertoxic form of diphtheria is myocarditis [1]. It can be explained by the presence of a plateau phase in the excitation of the cardiomyocytes, which prolongs the duration of depolarization, as compared to that in the cells of other excitable tissues. This is followed by tubular nephrosis [7], adrenal hemorrhage [8], and by neuritis and polyneuritis several weeks after, sometimes even after recovery [9]. This sequence is associated with the substrate specificity of the toxin to EF-2, which is normally present near the ribosomes and the rough endoplasmic reticulum. In neurons, these organelles are located only in the soma; the toxin enters the cell most often through axons and dendrites; in order to reach its substrate, the subunit a then uses intracellular mechanisms of protein transport from the projections to the cell body, i. e., retrograde transport. Use of such mechanisms has been reported for many toxins [10]. However, transport here is very

slow, approximately 1 mm/day, which is why the damage to the nervous system usually occurs at a later stage [9].

Nephrosis may be associated with the renal filter structure: the pores are located in its narrowest segment, and the glomerular basal membrane allows passage of non-negatively charged molecules weighting up to 69 kDa, which is associated with the presence of the negatively charged glycocalyx on the surface of the cell membrane [5]. Evidently, DT is filtered into the Bowman–Shumlyansky's capsule where it enters the proximal tubules by endocytosis facilitated by its interaction with the megalin-cubilin complex [5]. DT is an acidic protein, so the penetration described is possible only if a molecule has a strong positive pole that will be pulled by the glycocalyx. Subsequently, instead of being cleaved by lysosomal enzymes, the a subunit of the toxin penetrates the cytosol of the tubular epithelium, which leads to nephrosis [7].

The above confirms that characteristics of blood supply explain only the adrenal hemorrhage caused by DT [8]. The blood flow through the adrenal glands is extremely vigorous (three major arteries and approximately 25–30 arterioles). This makes the organ vulnerable to pressure changes and susceptible to thrombogenesis under conditions of extensive blood loss, toxemia and shock, when the blood supply to vital organs is amplified to the detriment of other less important organs [11].

CONCLUSIONS

The proposed integrated hypothesis explains both the mechanism of action of diphtheria toxin and its impact on the infectious process in general, which lends a better understanding of the pathogenesis of diphtheria. The proposed hypothesis provides a basis for improved methods of treatment of the hypertoxic form of the disease, and a framework to study the mechanism of action of other toxins.

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