THE METHODS OF PERFECTING THE SURFACE OF TITANIUM ALLOY-BASED ENDOPROSTHESES USED IN PEDIATRIC ONCOLOGY

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ABSTRACT

The rehabilitation of pediatric patients with oncology diseases localized in the maxillofacial area is a complex and long-term process. Most frequently, the resection area involves the maxilla or the mandible, which, in turn, impairs the functioning of the whole dentofacial system. The restoration of the integrity of the facial structures is the key task in the treatment of such patients. One of the main materials used for reconstructing the jaws is the titanium alloy. However, despite its beneficial properties and characteristics, there is a high risk of inflammation, encapsulation or failure of the endoprosthesis. The aim of the research was to analyze the data available up to date on the methods of perfecting the surfaces of titanium endoprostheses based on the published research works. After analyzing the articles devoted to the modification of the surface of titanium constructions used for endoprosthetics, for the period from 2008 until 2022 (n=41), we came to a conclusion that the modification of the surface of titanium endoprostheses results in an increase in its osteointegration, which decreases the risks of failure for the constructions.

Keywords: *titanium alloy; endoprosthesis; pediatric oncology; rehabilitation; jaw resection; plasma-electrolytic oxidation.*

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INTRODUCTION

Every year the number of oncological diseases worldwide grows. According to our data, at the Federal State Budgetary Institution “Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology” of the Ministry of Health of the Russian Federation (Dmitry Rogachev NMRC PHOI), for the time period of 2017–2022, a total of 118 patients aged from 3 to 18 years were admitted with various neoplasms of the maxillofacial area, of which malignant neoplasms were found in 49% and benign neoplasms were detected in 51%, with the tumor process located in the maxilla reported in 66% of the cases and in the mandible — in 34%.

Generally, the surgical treatment in cases of oncology diseases located at the maxillofacial area is accompanied by not only the functional impairment (respiration, chewing, swallowing, speaking), but it also results in significant esthetic problems [1]. The excision of the tumor focus together with growth center can cause the incomplete development of the jaws and severe secondary deformation.

The growth and development of the upper and the lower jaws, as well as the facial skeleton in general, in the opinion of a number of authors, depend on the correct anatomic ratio between them [2]. During the childhood and the adolescent age, when the development of the facial skeleton is not complete, the most important is to restore the integrity of the jaws and to stimulate growth in the remaining bone fragments. Early maxillofacial rehabilitation, when conducted timely, helps decreasing the extent of secondary deformation related to polyvisceral resections [3]. This is why early restoration of the defect after the excision of the tumor focus is an important aspect in reconstructive surgery.

There are multiple materials used for the restoration of the integrity of jaws: natural (auto-, allo- and xenotransplants) and synthetic (hydroxyapatite, tricalcium phosphate, chirulen, metals alloys etc.), mixtures of synthetic materials with the organic ones are also being used. The main objective of searching new artificial materials is to avoid using autobone transplants in pediatric maxillofacial surgery in order to preserve the donor area and to prevent complications. On top of that, the significant downside of autotransplants is the absence of growth potential in the bone tissue flap, while the individually adjusted construction made of artificial materials, for example

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МЕТОДЫ УСОВЕРШЕНСТВОВАНИЯ ПОВЕРХНОСТИ ЭНДОПРОТЕЗОВ НА ОСНОВЕ ТИТАНОВЫХ СПЛАВОВ, ПРИМЕНЯЕМЫХ В ДЕТСКОЙ ОНКОПЕДИАТРИИ

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АННОТАЦИЯ

Реабилитация пациентов детского возраста с онкопатологией, локализованной в челюстно-лицевой области, — сложный и длительный процесс. Чаще всего резекция затрагивает верхнюю или нижнюю челюсть, что в свою очередь нарушает функционирование всей зубочелюстной системы. Восстановление целостности лицевых структур является ключевой задачей при лечении таких пациентов. Одним из основных материалов для реконструкции челюсти является сплав титана. Однако, несмотря на его положительные свойства и характеристики, велик риск воспаления, инкапсуляции и отторжения эндопротеза. Целью исследования был анализ существующих на сегодняшний день данных по методикам усовершенствования поверхности титановых эндопротезов на основании опубликованных работ. Проанализировав статьи по модификации поверхности конструкций из титана, применяемых для эндопротезирования, за период с 2008 по 2022 год (n=41), мы пришли к выводу, что модификация поверхности титановых эндопротезов ведёт к повышению их остеоинтеграции, что снижает риски отторжения конструкций.

Ключевые слова: *сплав титана; эндопротез; детская онкология; реабилитация; резекция челюсти; плазменно-электролитическое оксидирование.*

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“growing” endoprostheses, would not prevent the growth of the facial skeleton in a child or undergo eventual atrophy [4, 5].

Within the facilities of the Dmitry Rogachev NMRC PHOI, the individually adjusted titanium constructions are being used for replenishing the jaw defects. With this, in case of failure in the vascularised bone flap, repeated restoration of the defect is carried out using the titanium prosthesis.

We have performed an analysis of 41 articles describing the modifications of the surface of titanium constructions used for endo-prosthetics, for the period from 2008 to 2022.

TI-6AL-4V ALLOW

The main alloy that is used for endoprostheses is Ti-6Al-4V. Its benefit is that it can be used in 3D-printers for creating any shape of endoprostheses.

The orthopedic implants must be biocompatible, must have proper mechanical properties, corrosion and wear resistance, also providing the osteointegration capabilities for their safe and effective usage [6].

Titanium is an extremely reactive material. Due to oxidation when interacting with water or air, it maintains its main characteristics and resistance to the effects of the environment. The oxidation film determines the biocompatibility of titanium. Due to the presence of negatively charged oxygen, there occurs the fixation of the bone morphogenetic proteins (BMP), of blood proteins and free calcium, promoting to the formation of the bone tissue matrix. Ti-6Al-4V alloy has high mechanical resistance with its torsional-axial characteristics being similar to the ones of the normal bone [7]. However, despite all the beneficial properties and characteristics of this metal, titanium endoprosthesis is a foreign body in the organism of the patient, which, in turn, can result in acute or chronic inflammation, fibrous encapsulation and developing granulation tissue. In order to solve this problem, the biomimetic approach is being used: changes are made in the structure and in the content of the implant surface, making it more compatible with the human tissue. This allows for achieving the biochemical and biomechanical compatibility and stimulates the osteointegration of the endoprosthesis into the bone tissue [8].

PLASMA ELECTROLYTIC OXIDATION

The promising methods of creating inorganic layers on the surface of implant include the techniques of electrochemical anodising, from which, a method of plasma electrolytic oxidation (PEO) can be highlighted, that forms (on the surface of titanium and its alloys) a conversion oxidation layer, showing high degree of adhesion [9]. The PEO mechanism includes the effect of microdischarges, multiple times penetrating and melting the oxidation layer, which results in the formation of a well-developed porous surface [10]. Such an approach allows for getting the surfaces with a unique morphology, which provides smooth modification of the modulus of elasticity from the metallic implant to the bone, increasing the mechanical compatibility. When treating the metal surface in a medium containing calcium and phosphorus, it becomes possible to obtain a surface, containing bioactive inorganic crystalline phases — hydroxyapatite, tricalcium phosphate, tetracalcium phosphate and perovskite [11]. The highly fractal structure of the PEO coating allows for applying various functional organic components, acting as a sub-layer, increasing the adhesion, and as a carrier for organic substances. For the purpose of forming a porous superficial layer with calcium phosphate compound on the surface, as an electrolyte component, calcium-containing salts are being used with a Ca/P ratio similar to the one found within the human bone tissue [12, 13].

BIOLOGICALLY ACTIVE COATINGS BASED ON RGD

Together with the PEO, for the purpose of improving the implant osteointegration, biologically active substances can be used that are based on the RGD tripeptide (arginine-glycine-aspartic acid), which is the ligand of integrins — one the major proteins of the intercellular matrix. The introduction of phosphonate groups increases the adhesion of the molecules to the surface, but the smooth metallic surface can not provide long-term retention of the biomolecules [14].

The Ti alloy, the PEO coating and the RGD pore filler can provide the necessary mechanical, physical and chemical properties of the implant [15]. In the research conducted by E.V. Parfenova et al. [15], it was shown that the combination of PEO coating and RGD-modified bisphosphonic acid applied to the nano-Ti, results in an increase in the number of proliferating cells by 45% comparing to the non-coated nano-Ti and by 66% comparing to coarse-grain Ti. It should be mentioned that this research included the use of cell lines of human pulmonary fibroblasts, the mesenchymal stem cells of human adipose tissue and the human osteosarcoma cells, which are very resistant to toxic effects, which can not precisely reflect the interaction of the normal bone tissue cells with the said materials.

The *in vitro* researches have demonstrated that the bioactivity of the molecules depends on the structure of the anchor and the linker. For example, RGD derivatives with short bisphosphonate anchors and a linker consisting of bone morphogenetic proteins (BMPS), as well as the molecules with the linker containing a cyclohexyl fragment, increase the cell proliferation at the PEO-modified titanium [10]. Upon the analysis of literature data, no pathological effects were found that are related to the interaction with the RGD.

ANTIBACTERIAL COATINGS

The use of endoprostheses oftentimes results in complications, resulting in their instability. The most common reason of implant failure and loss of surrounding tissues is the infection, caused by forming biofilms on its surface, upon the development of which, almost in half of the cases (51%), extraction of the endoprosthesis may be required [16].

The ingress of infection depends on multiple factors: the microorganism species, the status of the immune response in a patient, the procedure and the technique employed during the surgical intervention, the construction of the implant and the antibacterial prophylaxis used.

It was proven that, even in case of scheduled surgery, the sterility of the operating room decreases within the first several hours of surgery [17, 18], while in the majority of cases the quite low bacterial burden, ultimately present during the surgery, can be generally overcome by the immunological protection system and by systemic antibiotic prophylaxis [19]. However, some patients after the surgical intervention may develop an infection, especially those with concomitant diseases, elevating the risk of infection by a factor of 20 comparing to the population of relatively healthy patients [20]. In the same way, it was shown that the most complex surgical procedures and methods are more dangerous in terms of septic complications [21].

The characteristics of the implant, for example, its dimensions, shape, material and intended application, also play an important role [22]. In order to decrease the rate of developing infections related to the implantation, local antibacterial prophylaxis can be used, for example, the bone cement saturated with antibiotics [23].

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With this background in mind, the methods were proposed of creating a surface of the biomaterials, capable of preventing the bacterial infection by means of using the surface biofunctionalization based on constructing the chimeric peptides with antibiotics.

The efficiency of TiBP1-GGG-AMP and TiBP2-GGG-AMP bifunctional peptides was evaluated both in the solution and on the solid surface of the titanium base in terms of counteracting *Streptococcus mutans*, *Staphylococcus epidermidis* and *Escherichia coli*. It was found that the surfaces modified using chimeric peptides, significantly decrease the bacterial adhesion to all three bacteria comparing to clear titanium. The research results show that surface modification by means of constructed biomolecules consisting of antimicrobial and titanium-bindings peptide domains represents a promising approach for preventing the bacterial infection development on the surfaces of the implants [24].

Another attractive approach for the prevention and treatment of implantation-related infections is coating the endoprostheses with vancomycin. The antibiotic coating was releasing 82.7% of the total vancomycin contained within the coating, as shown by *in vitro* research. A biphasic type of antibiotic release was demonstrated with an initial burst in day 1, followed by slow and controlled release lasting 28 days. No cytotoxicity of the vancomycin-containing coating was observed during the *in vitro* research. Titanium implants, coated with vancomycin, were active in the treatment of implantation-associated infections, as shown by *in vivo* research [25]. However, microbial resistance should be taken into consideration, as well as allergic reactions in susceptive individuals. In such cases, in a context of individually adjusted medicine, the optimal variant can include coating the titanium endoprosthesis with a matrix, into which, an antimicrobial agent should be introduced directly before surgery. In order to solve this problem, in recent years, the research works were carried out on modifying the surfaces of implanted materials, in particular, coating it with carbon nanotubes [26]. However, data exist indicating the risk of toxicity related to its size, surface charge, chemical composition, reactivity, chemical and crystalline structure, shape, solubility and agglomeration degree. Moreover, nanomaterials may cause oxidative stress and may impair the phagocytosis inside the cells, decreasing the viability of cells and suppressing their growth [27].

The alternative to using antibiotics may include the use of zinc (Zn). It is well known that zinc is an important microelement for humans, capable of performing various functions in the bone tissue, such as the participation in the DNA synthesis, the activity of enzymes, the metabolism of nucleic acids, the biomineralization and the hormonal activity, with all these being said, zinc exhibits excellent antibacterial properties [28]. The inclusion of zinc into bioglass and bioceramics within the Ca-P and Ca-Si systems for improving their mechanical properties and the interactions of cells with the materials is deemed quite promising [29–32]. A research by H. Zhang et al. [33] has shown that the TiO_2 coating, containing zinc and obtained by means of using the PEO method, exhibits antibacterial effects on *Staphylococcus aureus and Escherichia coli*. Zinc was evenly distributed along the surface, not affecting the microstructure, the roughness, the phase composition or the chemical state of the TiO_2 coating. High efficiency was demonstrated for TiO_2 coatings containing zinc in terms of inhibiting the bacteria, due to slow release of zinc ions. In turn, a research by M. Shimabukuro [34] has shown that the antibacterial effect of zinc on the surface of the implant manifests itself after 28 days of incubation in the physiological saline solution. These specific results can help controlling the antibacterial effects at the surface of the implant in the long-term perspective.

The porous and nanostructurized TiO_2 coatings with an addition of zinc show excellent antibacterial activity and the capability to stimulate osteogenic differentiation, which gives ground for considering them the promising materials for reconstructive maxillofacial surgeries. At the same time, the effects of zinc on the tumor cells is insufficiently studied, also, the incorrectly adjusted zinc dosage can be cytotoxic [35]. This method requires further research activities, especially when used in patients with oncology diseases.

BONE MORPHOGENIC PROTEINS

Another promising approach for increasing the osteoinductivity of bone implants and for increasing the connective tissue regeneration is creating biocomposite materials containing growth factors. Bone morphogenetic proteins (BMP) are considered the most important factors for bone and cartilage regeneration. They affect the cell membrane, regulating the growth, differentiation and apoptosis of various cell types, including osteoblasts, chondroblasts, neural and epithelial cells. BMP can be found in the extracellular connective tissue matrix, containing osteoprogenitor and mesenchymal cells. For the fixation of proteins on the surface of the implant, synthetic, biological, mineral or biocomposite polymers are being used as a “carrier”. The main role of the BMP “carrier” after the implantation is keeping these osteoinductors at the area of their biological effects within a long-term and clinically justified period of time. Long-term release of small quantities or initial burst of significant quantities of BMP extremely negatively affects the regeneration processes [36].

In a research by Z. Liu et al. [37], microspheres were developed that contain the endothelium growth factors and the bone morphogenetic protein 2, with further applying them to the porous titanium alloy manufactured by 3D-printing. The microspheres were encapsulated into the gelatin coating and used for creating a composite frame, which has shown good results when tested in rabbits. The system provides sequential release of growth factors, promoting to the osteogenic differentiation and osteointegration.

Despite the positive results of scientific-clinical research works on studying the bone morphogenetic proteins, a number of questions within this issue remains unsolved. The main of them are the selection of an effective technology for obtaining the BMP; the selection of an adequate biodegradable carrier for the BMP; finding the variants of BMP chemical fixation on the biodegradable carrier; determining the clinically effective dosage of BMP depending on the etiology, the location and the severity of the pathological process; finding the ways of decreasing the commercial cost of BMP. The experimental and clinical researches of BMP are currently being carried out practically in all the countries of the world. The participation of large number of leading foreign scientific-research centers, as well as the addition of significant material and financial resources gives hope of further effective solving these problems and of successful application of the said osteoinductor in practical medicine [38]. However, it is worth noting the impossibility of using BMP in cases of cancer diseases: data exist showing that BMP is highly expressed in various cases of cancer and promotes the proliferation, migration, metastatic spreading and invasiveness of various types of cancer cells [39, 40].

CONCLUSION

After analyzing the domestic and foreign literature data, a conclusion can be drawn up that one of the promising directions is the development of bone-tissue engineering, which allows for studying the use of bioactive materials with antiinflammatory and regenerative properties. However, this is a long process, requiring larger numbers of cost-intensive scientific research with developing complex technological protocols. It will take plenty of time until such materials become accessible in Pediatric oncology. With all of these, the factors of utmost importance shall include the availability of such technologies and the possibility of their implementation in the medical institutions.

In the modern era, using reconstructive materials made of titanium alloys, including their use in children with oncology diseases, have already shown good results. The modification of the surface of titanium reconstructive materials for the purpose of increasing the osteoinductive, osteoconductive and antimicrobial properties shall allow for decreasing the number of repeated surgeries, for decreasing the risks of developing infections and implant failures, as well as for preventing the development of secondary deformations and, hence, for improving the quality of life of the pediatric patient.

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