Biotechnology in medical application of biocomposite materials for optimization of bone tissue regeneration

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Abstract. A combination of properties of osteoplastic biocomposite materials, including biological compatibility and biodegradability, puts them in the category of high-tech materials of the 21st century. Biomedical technologies related to the development of materials and devices for reconstructive surgery are particularly promising areas of application of osteoplastic materials. Despite the apparent progress of reconstructive oral surgery, the closure of postoperational extensive alveolar bone defects remains a pressing medical and social problem, for example, plasmocytoma. This disease implies not only treatment by hematologist-oncologist, but also surgical removal of osseous defect followed by its closure, which is a difficult prognostic and time-consuming process. No data on the long-term results of monitoring such patients are available in the literature.

1. Introduction
The problem of complete closure of postoperative bone defects is relevant since it is related to the structural features of the alveolar bone tissue, a rather compact arrangement of the highly mineralized fibrous matrix, which determines a significant mechanical strength of facial bones [1, 2]. This, in turn, causes certain types of lesions as a result of various degenerative and destructive processes in the maxillofacial bone tissue and during surgery, which can exceed the strength of the bone tissue [3, 4].

The data from modern studies allow us to assert that osteoblastic cells cannot completely replace the tissue defect that always occurs under the impact of various damaging factors despite their high reparative properties [5, 6]. This, in turn, leads to a significant de-escalation of the inherent regenerative abilities of bone tissue cells and causes the so-called osteogenic insufficiency. This is a rather serious problem, since it entails the occurrence of fibrosis, i.e. replacement of defects in the maxillofacial bone tissue with reticulofibrous tissue, which requires surgical intervention with the use of specialized osteoinductive bone replacement materials [7, 8].

2. Purpose of study
The aim was to perform clinical study of the osseointegration of osteoplastic biocomposite materials with hydroxyapatite inclusion during intraoperative filling of maxillofacial bone defects when removing plasmacytoma foci. The study also aims to reveal the ability of biocomposite osteoplastic materials based on hydroxyapatite (HA) to stimulate osteoblast transformation of poorly differentiated cells under favorable conditions (neoangiogenesis).
3. Relevance of study
In modern reconstructive surgery, osteoplastic materials must meet the following requirements: the highest degree of biocompatibility, osteogenicity (contain cellular sources); osteoinduction (initiate osteogenesis); osteoconduction (serve as a matrix for new bone formation); osteoprotection (replace bone by mechanical properties) [9, 10]. The medical market for bone graft materials is rather wide and offers a wide range of modern materials (metals, ceramics, natural materials based on collagen and chitosan, composite ceramics mixed with natural and synthetic polymers). However, none of these fully meets the criteria. This is why the study and development of new osteoplastic materials and devices that are designed based on these materials are of high relevance and demand [11, 12]. HA-based osteoplastic biocomposite materials are most widespread in maxillofacial reconstructive surgery, but the data indicating the effectiveness of HA devices used in vivo for bone tissue defect restoration are rather poor. This fact determined the area of our study to focus on studying the integration of the Kolapol-KP3 material as an optimal osteoplastic material used for maxillary defect repair in treatment of tumors and tumor-like lesions in the oral cavity and periodontal diseases in patients with plasmacytoma. Osteoplasty as the main method of biostimulation of osteogenesis has been known for a long time, and it is used in reconstructive surgery of the oral cavity and periodontal tissues to provide substitution, support and osteoinduction [13, 2].

The best type of osteoplasty is bone grafting using autografts (autogenous tissue) since they are free of antigenic properties, show better adaptation and transformation, and surgical intervention is relatively simple and inexpensive. Nevertheless, particular features of obtaining bone tissue for autoplasty in surgical dentistry and its use can cause complications even in well-managed cases. We have proposed and successfully tested improved options for HA-based biocomposite materials on patients with plasmacytoma. Among synthetic biogenic materials, the most popular are different types of phosphorus-calcium compounds, both foreign and Russian, which recently have been widely used in traumatology, maxillofacial surgery and dental practice. The main disadvantage of foreign osteoplastic materials is their high cost. Due to the variability of hydroxyapatite-collagen compositions and different size of hydroxyapatite particles (from 1 µ to 1 mm), materials based on them exhibit different properties.

In maxillofacial surgery and dental practice, HA-based preparations are used to stop bleeding and replace defects in operations on maxillary bones. In recent years, a sufficient number of studies have been carried out on each of these materials, and the results were published in Russian and foreign journals. The experience obtained in clinical studies suggests that domestic HA-based preparations can replace more expensive foreign alternative drugs.

4. Materials and methods
In outpatient conditions, we used conventional and additional methods, including computed tomography, to examine 200 patients aged 35–60 years with pathology of the oral cavity and periodontal tissues, among them 3 patients with plasmacytoma (figure 1), and performed operations on them. A histological examination of the specimens obtained was carried out in the histological laboratory of Novgorod Regional Clinical Oncological Dispensary.
As osteoplastic materials, we used HA-based materials, which are characterized by a sufficiently high biocompatibility with human tissues, are bioinert and do not cause rejection. The biocomposite material Kolapol-KP3 (NPK Polystom) enhances osteogenesis and stimulates healing of bone wounds. This material belongs to non-toxic substances and does not cause long-term adverse effects (inflammatory, allergic reactions, mutagenic and immunomodulatory effects, does not affect gestation course and fetal development). Kolapol-KP3 has been widely used in recent years in traumatology, surgical, orthopedic and dental practice to infill bone cavities emerged after resection of cysts and tumors, sequestrectomy, in repeatedly operated patients with chronic osteomyelitis (including those with complicated pathological fracture). When filling cavities of big size (> 5 cm³), it can be used together with Hydroxyapol (powder and granules) and Indost gel.

In our study, we used fragments 20x8x7 mm in size, weighing 0.15± .05 g, white or almost white (TU 9391-003-77330104-2011). It can be manufactured in antimicrobial performance: L for lincomycin hydrochloride, M for metronidazole.

The main advantage of using a biocomposite material in patients with plasmacytoma is the absence of an immune response of the recipient bed, good integration and further remodeling of the alveolar bone tissue [14].

Method of application: After surgical removal of the pathological focus, it was placed in formalin solution and sent for pathological examination to the Department of Pathological Anatomy of Novgorod Regional Clinical Oncological Dispensary. The osteoplastic material was removed from the sterile package with sterile forceps, if necessary, an additional part was cut off with sterile scissors and inserted into the wound or bone defect to fill 40–60% of the cavity volume. The mobilized flap was placed on the wound, and then it was closed with continuous suture tightly enough to bring the wound edges together using monofilament threads. The implanted material was not removed, since it was completely resorbed and replaced by bone tissue.

The patients were prescribed antihistamines, non-steroidal anti-inflammatory drugs, and antibiotics. A thorough medical treatment of the wound was carried out; a bandage of keratoplastic preparations was applied (solcoseryl in the form of a dental adhesive paste).

The advantages of this osteoplastic method are as follows: the absence of a donor site that minimizes postoperative complications (bleeding, hematomas, edema, pain, paresthesias, etc.), a sufficiently tight contact between the bone bed and the biocomposite material due to its soaking with blood; possibility of one surgical access only.

**Figure 1.** Patient, 50 years old. Maxillary alveolar bone destruction. Axial plane.
5. Results
The tested methods for optimizing bone grafting and for inducing osteosynthesis showed high osseointegration (figure 2) and positive and sufficient long-term results of clinical studies of patients with plasmacytoma. The use of biocomposite osteoplastic materials based on hydroxyapatite is highly efficient and allows significant improvement of the quality of reparative processes and osteosynthesis. A relative simplicity and easy application of HA-based biocomposite materials enable their use in medical institutions of different levels.

Figure 2. Full integration of the osteoplastic material. Axial plane. Control after 3 years.

6. Conclusion
In terms of their transplantation properties, biocomposite osteoplastic materials based on hydroxyapatite can occupy a leading position among other osteoplastic materials, which is primarily due to the lack of histoincompatibility, since these materials do not contain protein fractions. It is beyond argument that the success of any operation directly depends on the removal of a pathological focus, but full integration of biocomposite osteoplastic materials, their mutual adaptation with the recipient bed are also important for complete closure of bone tissue defects. Different methods and techniques are used to repair postoperative bone tissue defects. However, methods that provide optimal mechanical and biological conditions for separative osteogenesis are most preferable to improve the quality of surgical interventions on the alveolar bones and periodontal tissues. This, in turn, offers new opportunities for further research into medical biotechnology and biomaterial integration.

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