Original Article

Reparative-regenerative features of bone tissue in experimental animals treated with titanium implants

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ABSTRACT

Many researchers are involved in the study of the importance of the material for the manufacture of implants and the influence of these materials on the reparative processes in bone tissue. Metal alloys indicate their high level of influence on the oral mucosa. It is safe to say that studying the effect of implants on body tissues in the future will minimize the number of complications and strengthen the processes of bone remodeling. In this article, we conducted an experiment on Wistar rats with the installation of implants and studied the reparative and regenerative features of bone tissue when using Grade 4 pure titanium implants, as well as Ti6Al7Nb and Ti6Al4V titanium alloys. During the experiment, we determined the best material for the manufacture of dental implants. So, we found that the use of Ti6Al7Nb alloy showed rejection in 87.5% (28 rejections) up to 30 days. The use of Ti6Al4V showed on day 20 rejection of 46.87%% (15 rejected) implants on day 25 (3 individuals) 9.37%% and 43.76% of implants took root in the rat oral cavity. The use of Grade 4 implants showed a pronounced process of bone remodeling in rats, relative to other samples used. All implants were covered with mucosa without any inflammatory processes. Up to 30 days, rejection occurred in 6% of individuals, and 94% of implants took root.

Keywords: Implants, Dentistry, Titanium nanoparticles, Materials, Oral hygiene

Introduction

A fairly large accumulated experience of using the dental implantation method in the modern world not only reveals the main advantages, but also makes it necessary to study the complication, both at the stages of prosthetics and in the future. The use of dental implants solves a significant part of the problems in the case of partial and complete absence of teeth, plays a crucial role in restoring the function of chewing, and helps in correcting and improving the aesthetics of the dentition, smile, and face as a whole [1, 2]. Many researchers have wondered about the importance of the material for the manufacture of implants and the influence of these materials on the reparative processes in bone tissue [3-7].

In Russia, dental implants are made of titanium grades B 1 0 and B 1 00. In other countries, these titanium grades are called commercial, or Grade 1-4 (Ti6Al4V). Since aluminum and vanadium contribute to the formation of an oxidized film in tissues, nano titan (Nano Grade) was started to be used, the length of the molecule of which corresponds to 1 nm, which is equal to the length of DNA [8, 9]. The surface of the "Nano Grade 4" nano titan has a greater roughness compared to implants made of coarse-grained titanium. The implantation of nano titan does not cause acute and chronic toxic reactions in the body of animals, titanium does not accumulate in the blood and parenchymal organs [10]. Implantation of nano titan into the body of experimental animals does not cause any negative reactions and does not affect the biochemical and immunological

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parameters of the blood. Nanotitan does not react with bone tissue and has a high osseointegration property. The formation of bone tissue in the intertrabecular space of the spongy bone occurs 6 months after titanium implantation [11].

Ti6Al4V alloy is the most versatile in use, including prostheses in surgery. BT6 (Ti6Al4V) refers to two-phase ($\alpha + \beta$)-alloys of the martensitic class with a small amount of β-phase, the presence of which determines their ability to harden heat treatment. This alloy is alloyed with aluminum in an amount of 5.3-6.8 wt.% and vanadium in an amount of 3.5-5.3 wt.% [12]. Titanium and its alloys meet the requirements for materials used in dental implantation in terms of chemical and mechanical properties. They are characterized by high elasticity and low density, so their strength is higher than that of other metals. When using titanium alloys with aluminum and vanadium, the strength of implantation structures increases [13, 14].

In previous studies, there are indications of the influence of bad habits and comorbid pathology on the condition of the oral cavity with metal prostheses installed [15-18]. Studies of the effects of metal dentures on the human body indicate that metal ions released into the oral cavity, due to the significant permeability of the oral mucosa, metal alloys resorbed by it in the oral cavity are subjected to electrochemical corrosion, possible galvanism reactions, resulting in diseases such as galvanosis, lichen planus, candidiasis [19, 20]. Galvanic processes caused by dissimilar alloys should be differentiated from general somatic diseases [21, 22].

Not only the materials from which the implants are made and their supra structures can cause inflammation in the tissues, but also other factors. This is the prevalence of inflammation in the gum around implants with the possible development of mucositis and bone resorption (peri-implantitis) [23]. In the absence of treatment with the elimination of inflammation, and restoration of lost bone tissue, periimplantitis ends with the disintegration of the implant [24, 25]. Almost all studies aimed at the prevention and treatment of mucositis and peri-implantitis indicate a negative role of insufficient oral hygiene. Peri-implantitis is one of the most common complications of dental implantation and can manifest itself both during the period before the fixation of permanent prostheses on implants and after [26]. Two mechanisms of development of peri-implantitis are considered. One of them is an overload of bone tissue due to an insufficient number of implants and the second is insufficient oral hygiene, so the efforts of implantologists are aimed at optimizing the hygienic condition of the mouth [27].

Agrawal *et al*. (2018) found that hygienic and periodontological indicators after preimplantation dental and periodontal sanitation deteriorate by the time the implants are opened [28]. Before the replacement of temporary prostheses with permanent ones and after three months of the functioning of prostheses on implants, which necessitates professional oral hygiene before these stages, including the use of herbal extracts with pronounced biological activity [29-32].

It is safe to say that studying the effect of implants on body tissues in the future will minimize the number of complications and strengthen the processes of bone remodeling.

The main objectives of the article were:

1. To develop and experiment on Wistar rats with the installation of implants.
2. To study the reparative-regenerative features of bone tissue in experimental animals when using Grade 4 pure titanium implants, as well as Ti6Al7Nb and Ti6Al4V titanium alloys.
3. To determine in an experiment on rats the best material for the manufacture of dental implants.

Materials and Methods

Experimental methods

We implanted Grade 4 pure titanium, Ti6Al7Nb, and Ti6Al4V implants in rats. Work with animals (maintenance, setting up experiments, and removing them from the experiment) was carried out following the European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes rules. Permission to conduct experimental studies on white laboratory rats of the Wistar line was received by the Ethics Committee of the North Ossetian State Medical Academy on November 29, 2019, Protocol No. 9.7.

The studies were carried out on 53 healthy Wistar rats, five of which dropped out of the experiments, and 96 implants were installed in the remaining 48 rats (2 implants on the lower jaw of each rat). All rats were divided into three groups, 16 in each. Grade 4 pure titanium implants were inserted into the animals of the first group, and Ti6Al7Nb and Ti6Al4V titanium alloys were inserted into the second and third groups, respectively. On days 7 and 14 after the implants were installed, 5 rats from each group in a state of anesthesia and narcological sleep were withdrawn from the experiment. Sedation was achieved by intraperitoneal administration of a general anesthetic – zoletil (France) at a dose of 0.1 ml / 100g for morphological studies of the condition near the implanted bone tissue. The remaining 6 rats in each group were removed from the experiment on the 30th day after implantation.

Morphological methods

We carried out a comparative morphological assessment of osseointegration of bone tissue on animal models of Grade 4 pure titanium implants, Ti6Al7Nb, and Ti6Al4V titanium alloys. The materials for the study were fragments of soft tissues excised from the alveoli at the implant site. The material was fixed in 10% buffered formalin, and pouring into paraffin was carried out in the Sakura Tissue-Tek VIP 5 Jr apparatus. using isopropanol. The sections were prepared using a Sakura microtome, staining was carried out with hematoxylin and eosin using the Thermo Scientific Shandon Varistain 24-4 apparatus, as well as antibodies to Ki 67, vimentin, CD 31, CD 34, and CD 45 using Ventana Bench Mark ultra and Thermo scientific Autostainer 360 stainers

[33]. Studies of the stained preparations were carried out using LEICA DM 1000 and Zeiss Axioscope light microscopes. Photo documentation was carried out using the Axiocam ERC 5s video camera and the Zen (Zeiss) program [34].

We determined the content (%) in Ki 67+ cells (expression in nuclei), the volume percentage of vimentin+ structures, as well as the percentage of CD 31+ and CD 34+ structures and CD 45+ cells. Volumetric vimentin was determined using an Avtandilov grid in 10 *x*200 or *x*400 fields of view, depending on the structures being determined, with the calculation of the average value for the drug and the average value for groups of animals.

The largest individual under sedation (zoletil) underwent dental computed tomography. The place of possible implantation in rats on the lower jaw in the lateral sections was chosen. The central incisors remained intact so that the animal could eat and live normally. After implantation, all individuals underwent antibiotic therapy for 5 days with intramuscular administration of ceftriaxone (Russia) at a dose of 5.0 mg/100 g twice a day. After the injection and then for another 9 days (a total of 14 days), the oral cavity was also washed with a syringe in a volume of 1.0 ml with a 0.05% solution of chlorhesidine digluconate.

Statistical methods

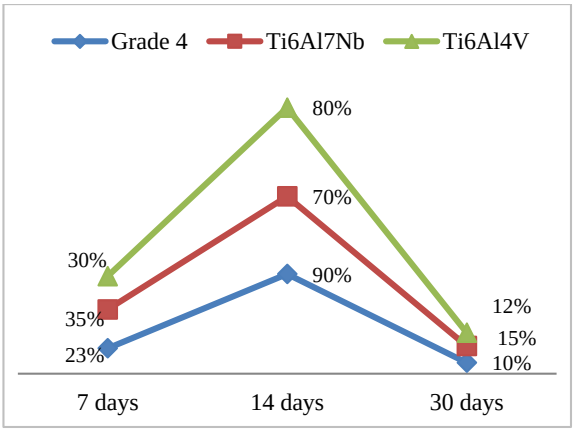
Statistical processing of the obtained results was carried out using the parametric method of comparing averages and conducting correlation analysis.

Results and Discussion

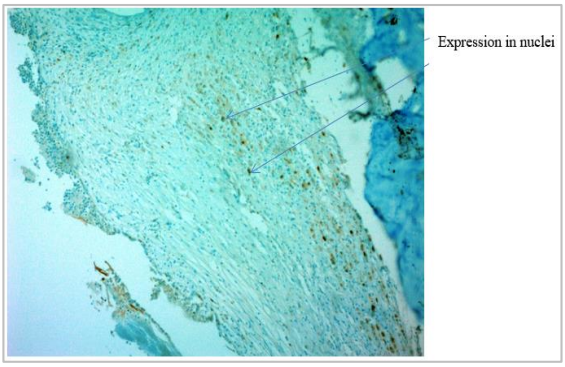
The measurement of the lower jaw, the width, and the length of the jaws allowed us to determine the size of the future implant 1.5 x 6 x 1.5 mm. We turned to the company "KONMET" with the question of providing us with implants made of various alloys for the experiment. Having chosen for implantation orthodontic screw aggressive implants "KONMET", which is completely suited in size. 3 types of implants were selected: Grade 4 (golden); Ti6Al7Nb (green); Ti6Al4V (silver). The question of choosing to install implants by machine or by hand (with a surgical screwdriver) remained relevant. We settled on the manual method of installation since the installation of implants was jewelry in nature (mm, nmm). The production of a surgical template for rats was not possible, since the synchronization of 3D printing on the printer by multispiral computed tomography (MCT) gave an error, and the use of an unprinted scan when drying the animal cavity using the MEDIT LINK program turned out to be impossible.

Under sedation (at a dose of 0.1 ml / 100g), a drug (zoletil) was injected under the skin. The rat's oral cavity was treated with a solution of 0.05% chlorhexidene digluconate and 3% hydrogen peroxide before surgery. Using a ZEIZZ f 170 dental microscopes at magnifications of 1.6 and 2.5 using a "KONMET" surgical screwdriver, we installed 2 implants made of different alloys on both sides in the lateral parts of the lower jaw body. Implants were installed in the body of the jaw along its length. When implantation was installed, primary stabilization of the bone tissue implants of the experimental animal was achieved. The implant head was completely visualized from the mucous membrane, and the implant was firmly located in the jaw bone. Due to the small size of the jaws of 4 rats, the implants were not deeply installed in the jaw. This was due to the exclusion of complications at the time of implant placement, as the bone of the lower jaw could crack.

The results of determining the volume fraction during Ki 67 staining (proliferative activity) are shown in **Figure 1**.



a)



b)

Figure 1. The results of determining the volume fraction during Ki 67 staining (proliferative activity): a) dynamics of proliferative activity (% of all nucleus cells that are determined in experimental sections) in rats of experimental groups, b) Ki 67 staining. Proliferative activity on the 30th day. General staining for all samples.

The analysis of **Figure 1** showed the following changes in proliferative activity: in the first group (Grade 4 pure titanium): 23% on day 7, 90% on day 14, up to 10% on day 30; in the second group (Ti6Al7Nb titanium alloy): 35% on day 7, 70% on day 14, 15% on day 30; in the third group (Ti6Al4V titanium alloy): 30% on day 7, 80% on day 14, 12% on day 30.

The results of determining the volume fraction during Vimentin staining (fibroblasts, connective tissue) are shown in **Figures 2 and 3**.

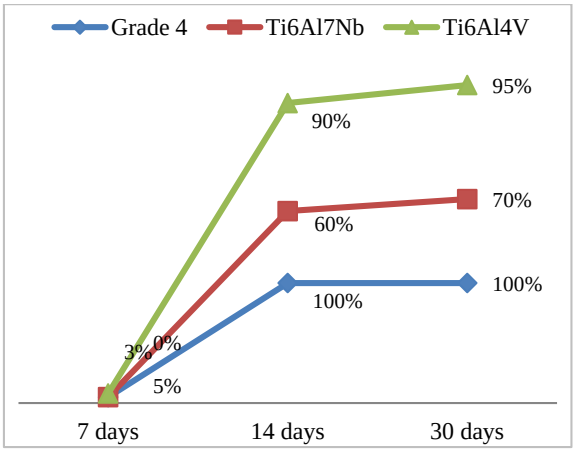
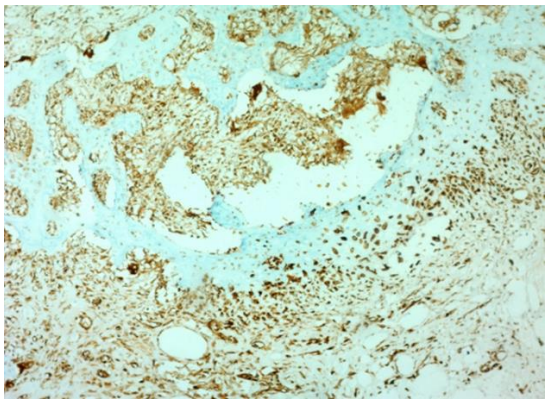
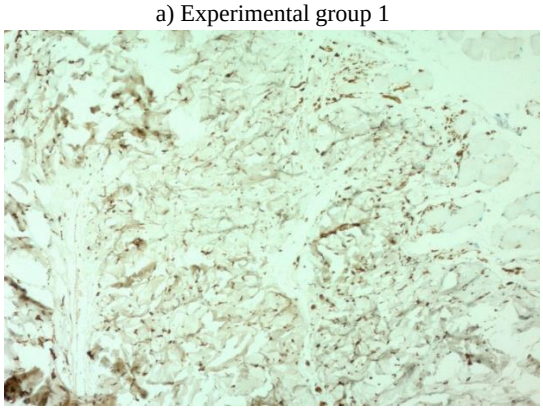


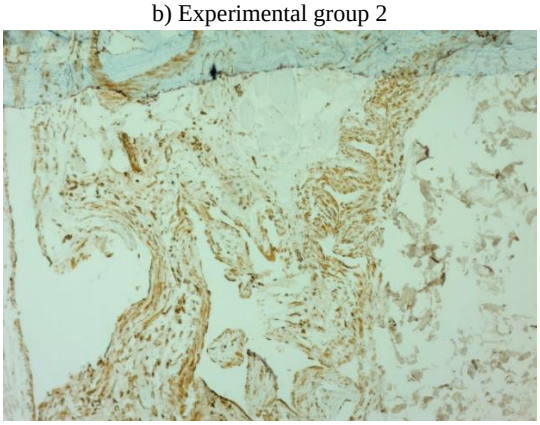
Figure 2. Dynamics of changes in fibroblasts and connective tissue (% of the area of the preparation determined using the Avtandilov grid) in rats of experimental groups



a) Experimental group 1



b) Experimental group 2



c) Experimental group 3

Figure 3. Staining of Vimentin (fibroblasts, connective tissue) on the 30th day.

Analysis of **Figures 2 and 3** showed the following changes in fibroblasts and connective tissue: in experimental group 1: 5% on day 7, 100% on day 14, 100% on day 30; in experimental group 2: 0% (not determined) on day 7, 60% on day 14, 70% on Day 30; in the experimental group 3: 3% on day 7, 90% on day 14, 95% on day 30.

The results of determining the volume fraction during CD31 and CD34 staining (vascular component, endothelial cell labeling) are shown in **Figures 4 and 5**.

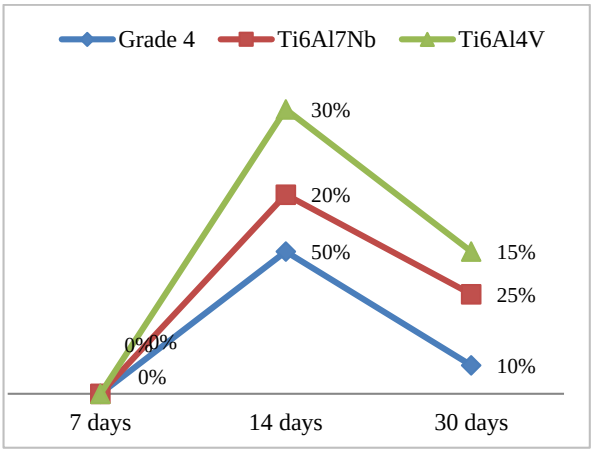


Figure 4. Dynamics of changes in vascular components and labeling of endothelial cells (% of the drug area) in rats of experimental groups

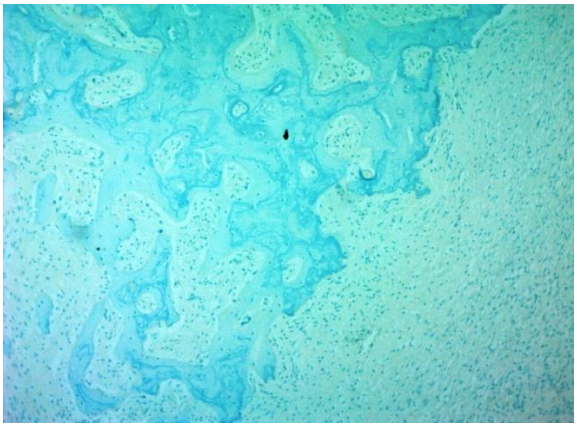


Figure 5. CD31 and CD34 staining. Vascular component, marking of endothelial cells on 30th day. General staining for all samples.

The analysis of **Figures 4 and 5** showed the following changes in vascular components and endothelial cell labeling: in the first experimental group 0% (not determined) on day 7, 50% on day 14, 10% on day 30; in the second experimental group: 0% (not determined) on day 7, 20% on day 14 day, 25% on day 30; in the third experimental group: 0% (not determined) on day 7, 30% on day 14, 15% on day 30.

The results of determining the volume fraction during CD45 staining (total leukocyte antigen, inflammation) are shown in **Figures 6 and 7**.

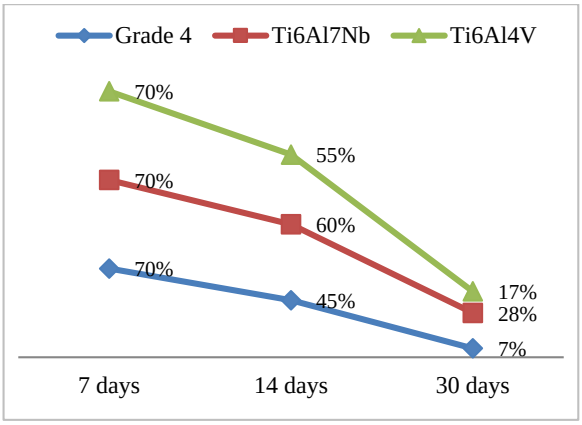
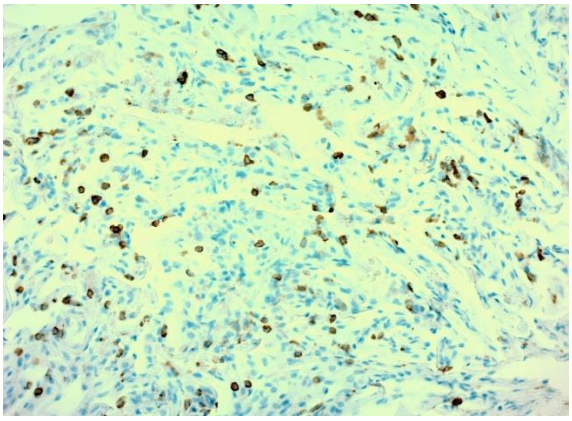
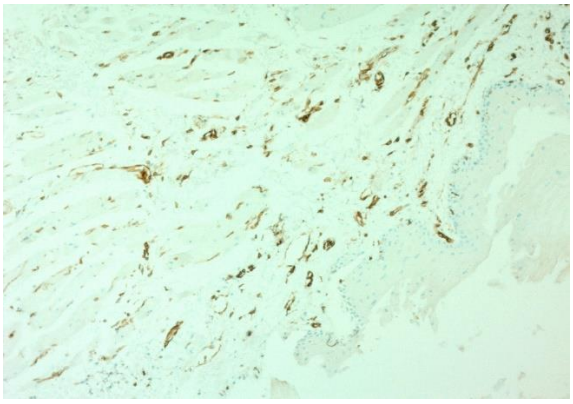


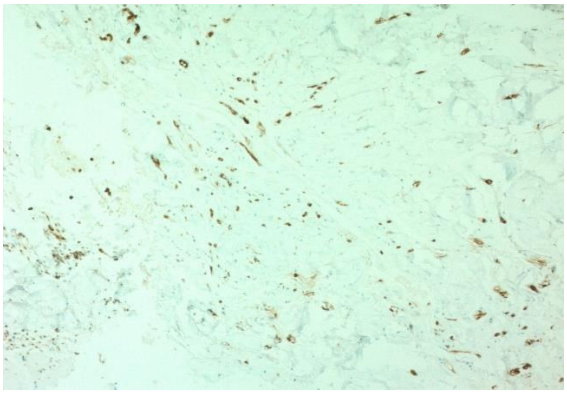
Figure 6. Dynamics of changes in total leukocyte antigen and inflammation (% of the area of the drug) in rats of experimental groups



Experimental group 1



Experimental group 2



Experimental group 3

Figure 7. CD45 staining (total leukocyte antigen, inflammation) on the 30th day. General staining for all samples.

Analysis of **Figures 6 and 7** showed the following changes in total leukocyte antigen and inflammation: in the first experimental group 70% on day 7, 45% on day 14, and 7% on day 30; in the second experimental group: 70% on day 7, 60% on day 14, 28% on day 30; in the third experimental group: 70% on day 7, 55% on day 14, 17% on day 30.

In experimental group 1, the volume fraction of Vim+ structures on the 7th day of the experiment is up to 5% of the drug, and the CD content of 45+ cells is up to 70%. The level of Ki 67 expression in Vim+ structures is up to 23%. The number of CD 31+ and CD 34+ structures has not been revealed. The volume fraction of Vim+ structures on the 14th day of the experiment is up to 100% of the drug, and the CD content of 45+ cells is up to 45%. The expression level of Ki 67 in Vim+ structures is up to 90%. The number of CD 31+ and CD 34+ structures is up to 50%. The volume fraction of Vim+ structures on the 30th day of the experiment is up to 100% of the drug, and the CD content of 45+ cells is up to 7%. The expression level of Ki 67 in Vim+ structures is up to 10%. The number of CD 31+ and CD 34+ structures is up to 10%.

In experimental group 2, the volume fraction of Vim+ structures on the 7th day of the experiment is up to 0% of the drug, and the CD content of 45+ cells is up to 70%. The level of Ki 67 expression in Vim+ structures is up to 35%. The number of CD 31+ and CD 34+ structures was not revealed. The volume fraction of Vim+ structures on the 14th day of the experiment is up to 60% of the drug, and the CD content of 45+ cells is up to 60%. The level of Ki 67 expression in Vim+ structures is up to 70%. The number of CD 31+ and CD 34+ structures is up to 20%. The volume fraction of Vim+ structures on the 30th day of the experiment is up to 70% of the drug, and the CD content of 45+ cells is up to 28%. The expression level of Ki 67 in Vim+ structures is up to 15%. The number of CD 31+ and CD 34+ structures is up to 25%.

In experimental group 3, the volume fraction of Vim+ structures on the 7th day of the experiment is up to 3% of the drug, and the CD content of 45+ cells is up to 70%. The expression level of Ki 67 in Vim+ structures is up to 30%. The number of CD 31+ and CD 34+ structures was not revealed. The volume fraction of Vim+ structures on the 14th day of the experiment is up to 90% of the drug, and the CD content of 45+ cells is up to 55%. The level of Ki 67 expression in Vim+ structures is up to 80%. The number of CD 31+ and CD 34+ structures is up to 30%. The volume fraction of Vim+ structures on the 30th day of the experiment is up to 95% of the drug, and the CD content of 45+ cells is up to 17%. The expression level of Ki 67 in Vim+ structures is up to 12%. The number of CD 31+ and CD 34+ structures is up to 15%.

Conclusion

In the preparations of all groups on days 7, 14, and 30, various stages of the formation of connective tissue at the implant site were determined. The use of immunohistochemical staining and determination of the volume percentage of vimentin, CD31+,

CD34+ structures, the average Ki content of 67 cells in connective tissue, and CD45+ cells in the preparations revealed a faster formation of connective tissue in animal preparations with pure Grade 4 titanium, which corresponded to the data obtained in the study of preparations stained with hematoxylin and eosin, as well as clinical observation during the experiment. When staining the preparations with Ki 67 antibodies, the content of Ki 67+ cells was determined in Vim+ structures, while the maximum content of Ki 67+ cells was noted on day 14 in the range of 70-90% with a tendency to increase this indicator in the preparations of the group with pure titanium Grade 4 (the maximum indicator was recorded mainly in the preparations of this group).

When assessing CD 31 and CD 34% structures, their maximum content was determined in the preparations of all groups on the 14th day of the experiment, also with a tendency to maximum values in the group with pure Grade 4 titanium.

The use of Ti6Al7Nb alloy showed rejection in 87.5% (28 rejections) up to 30 days. The use of Ti6Al4V showed on day 20 rejection of 46.87%% (15 rejected) implants on day 25 (3 individuals) 9.37%% and 43.76% of implants took root in the rat oral cavity. The use of Grade 4 implants showed a pronounced process of bone remodeling in rats, relative to other samples used. All implants were covered with mucosa without any inflammatory processes. Up to 30 days, rejection occurred in 6% of individuals, and 94% of implants took root.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: Work with animals (maintenance, setting up experiments, and removing them from the experiment) was carried out following the European Convention for the Protection of Vertebrate Animals Used for Experiments or Other Scientific Purposes rules. Permission to conduct experimental studies on white laboratory rats of the Wistar line was received by the Ethics Committee of the North Ossetian State Medical Academy on November 29, 2019, Protocol No. 9.7.

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