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Experimental and morphological rationale for applying a synthetic bone graft containing Hydroxyapatite and β -tricalcium phosphate in combination with a collagen sponge with polydeoxyribonucleotide in the treatment of mandibular bone defects

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ABSTRACT

Aim: To evaluate the effectiveness of the simultaneous use of a synthetic bone graft containing hydroxyapatite and β -tricalcium phosphate in combination with a collagen sponge impregnated with polydeoxyribonucleotide for the treatment of mandibular bone tissue defects through comprehensive morphological analysis of experimental material.

Materials and Methods: In this study, an experiment was conducted on 96 male rats of the WAG population aged 6 to 8 months. All animals were randomly divided into four groups. Group 1 included 24 rats in which a perforated defect was modeled in the region of the mandibular angle. Group 2 included 24 rats in which a perforated defect similar to that in group 1 was modeled in the region of the mandibular angle. The defect was filled with the synthetic bone graft «Biomim GT» (RAPID, Ukraine), which is composed of hydroxyapatite and β -tricalcium phosphate. Group 3 included 24 rats with a mandibular defect similar to those in groups 1 and 2. The defect was filled with a collagen sponge (DSI Dental Solutions Ltd., Israel) impregnated with polydeoxyribonucleotide (BNC Korea, Korea). Group 4 included 24 rats with a mandibular defect similar to those in the previous groups. The defect was simultaneously filled with the synthetic bone graft «Biomim GT» (RAPID, Ukraine) and a collagen sponge impregnated with polydeoxyribonucleotide. In groups 1 to 4, six rats from each group were sacrificed on days 3, 7, 14, and 28. Fragments of the mandible from the area of the modeled defect were used as material for morphological analysis. Histological, morphometric and statistical research methods were used.

Results: The authors' comprehensive morphological analysis of experimental material demonstrated an activation of reparative osteogenesis in the mandible in cases where the perforated defect was filled either with the synthetic bone graft «Biomim GT», containing hydroxyapatite and β -tricalcium phosphate, or with a collagen sponge containing polydeoxyribonucleotide. The therapeutic effect was more pronounced in the group treated with the collagen sponge impregnated with polydeoxyribonucleotide. However, neither of these treatment strategies led to the formation of fully mature bone regenerate by day 28 of the experiment. In contrast, the simultaneous application of the synthetic bone graft «Biomim GT» and the collagen sponge with polydeoxyribonucleotide resulted in a more active stimulation of reparative osteogenesis and contributed to the formation of a structurally complete bone regenerate by day 28.

Conclusions: Simultaneous filling of a bone defect in the mandible modeled in rats with the synthetic bone graft «Biomim GT», containing hydroxyapatite and β -tricalcium phosphate, and a collagen sponge with polydeoxyribonucleotide stimulates reparative osteogenesis and leads to the formation of a complete bone regenerate by day 28 of the experiment. The therapeutic effect is due to the rapid clearance of the defect cavity from blood fragments and alternatively changed tissues; active production and replacement within the regenerate of granulation, connective, and osteogenic fibroreticular tissues with the formation of lamellar bone tissue characterized by the presence of hematopoietic foci; decrease in the severity of inflammatory infiltration and hemodynamic disturbances in the tissues of the regenerate area.

KEY WORDS: synthetic bone graft, hydroxyapatite, β -tricalcium phosphate, polydeoxyribonucleotide, mandibular bone tissue defect, reparative osteogenesis

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INTRODUCTION

Among the bones of the craniofacial region, the mandible is particularly significant due to its crucial role in supporting dental structures and enabling essential functions such as mastication, speech, and maintaining facial aesthetics [1].

Mandibular bone tissue defects represent one of the key problems in modern dentistry [2]. Mandibular bone defects may arise from a variety of etiological factors. Minor defects are typically associated with tooth extraction or

low-impact trauma, whereas larger defects are commonly caused by severe traumatic injuries, degenerative conditions, congenital anomalies, or tumor resections [3]. These defects result in facial deformities, impair mastication and speech functions, and negatively impact both the physical and psychological well-being of patients, thereby significantly reducing their quality of life [4, 5].

The mandible is more difficult to reconstruct than other craniofacial bones due to its complex anatomical curvature,

irregular shape, presence of dentition, and essential role in oral function [5, 6]. The latter fact highlights the need to improve existing methods and develop new approaches for the treatment of patients with mandibular bone defects.

Polydeoxyribonucleotide is a bioactive form of polynucleotides, with molecular weights between 50 and 1,500 kDa, primarily sourced and refined from the sperm cells of trout (*Oncorhynchus mykiss*) or chum salmon (*Oncorhynchus keta*) [7]. Studies have shown that polydeoxyribonucleotide stimulates reparative osteogenesis [8, 9].

Our previous morphological study of experimental material, along with the findings of other researchers, has confirmed the effectiveness of using a synthetic bone graft containing hydroxyapatite and β -tricalcium phosphate in the treatment of mandibular bone tissue defects [10-12].

A promising approach to the treatment of mandibular bone tissue defects may be the simultaneous use of a synthetic bone graft containing hydroxyapatite and β -tricalcium phosphate in combination with a collagen sponge impregnated with polydeoxyribonucleotide. Our literature review revealed no reports of such a combination, which underscores the relevance of this study.

AIM

The aim of this study was to evaluate the effectiveness of the simultaneous use of a synthetic bone graft containing hydroxyapatite and β -tricalcium phosphate in combination with a collagen sponge impregnated with polydeoxyribonucleotide for the treatment of mandibular bone tissue defects through comprehensive morphological analysis of experimental material.

MATERIALS AND METHODS

In this study, an experiment was conducted on 96 male rats of the WAG population aged 6 to 8 months. All animals were randomly divided into four groups.

Group 1 included 24 rats in which a perforated defect was modeled in the region of the mandibular angle. The animals were anesthetized, and an incision was made in the soft tissues of the left submandibular region. A perforated canal-shaped defect with a diameter of 3.0 mm was created in the area of the mandibular angle using a spherical bur with a straight handpiece. After modeling the defect, the wound was closed using 4.0 polyamide sutures (Limited Liability Company «Research and Experimental Production Center «OLIMP», Ukraine).

Group 2 included 24 rats in which a perforated defect similar to that in group 1 was modeled in the region of the mandibular angle. The defect was filled with the synthetic bone graft «Biomin GT» (RAPID, Ukraine), which is composed of hydroxyapatite and β -tricalcium phosphate.

Group 3 included 24 rats with a mandibular defect similar to those in groups 1 and 2. The defect was filled with a collagen sponge (DSI Dental Solutions Ltd., Israel) impregnated with polydeoxyribonucleotide (BNC Korea, Korea).

Group 4 included 24 rats with a mandibular defect similar to those in the previous groups. The defect was

simultaneously filled with the synthetic bone graft «Biomin GT» (RAPID, Ukraine) and a collagen sponge impregnated with polydeoxyribonucleotide.

In groups 1 to 4, six rats from each group were sacrificed on days 3, 7, 14, and 28.

Fragments of the mandible from the area of the modeled defect were used as material for morphological analysis. The material was fixed in a 10% solution of neutral formalin (pH 7.4) for 24-48 hours, decalcified and carried out according to the generally accepted method and embedded in paraffin. Serial sections with a thickness of $4\text{-}5 \times 10^{-6}$ m were prepared from the paraffin blocks and subsequently stained with hematoxylin and eosin, as well as with picrofuchsin according to van Gieson.

The prepared microscope slides were examined using ZEISS Primostar 3 microscope (Carl Zeiss, Germany) equipped with an integrated color digital camera, and BRESSER Science TFM-301 Trino microscope with BRESSER Full HD camera (Bresser GmbH, Germany).

Morphometric analysis was performed using the Labscope software. In each case, five fields of view were examined at $\times 100$ magnification. Within the regenerate, the following parameters were quantified: specific volume (%) of blood and alternatively changed tissues; specific volume (%) of granulation tissue; specific volume (%) of connective tissue; specific volume (%) of osteogenic fibroreticular tissue; specific volume (%) of lamellar bone tissue with connective tissue present in the intertrabecular space; specific volume (%) of lamellar bone tissue with foci of hematopoiesis in the intertrabecular space.

Statistical analysis of the group data was performed using the PAST software (version 4.15, Natural History Museum, University of Oslo, Norway). Mean values between groups were compared using Student's t-test and the Mann-Whitney U-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

On day 3 of the experiment, overview light microscopy of the specimens revealed, in all groups, the presence of blood and alternatively changed epithelial layers, as well as fragments of muscle, connective, and bone tissues within the superficial and middle regions of the mandibular defect. The altered tissues were infiltrated with blood and exhibited diffuse polymorphic cellular infiltration consisting of neutrophilic leukocytes, monocytes, lymphocytes, mast cells, and macrophages. In groups 1 and 2, foci of immature granulation tissue were observed in the deeper regions of the defect cavity. In groups 3 and 4, granulation tissue of varying degrees of maturity and connective tissue were identified in the middle and deep regions. Both granulation and connective tissues showed signs of hemodynamic disturbances and focal-diffuse polymorphic cellular infiltration (Fig. 1). This infiltration included neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, osteoclasts, and fibroblast differon cells. Bone graft granules were identified within the granulation tissue in group 2 and within both granulation and connective tissues in group 4 (Fig. 1).

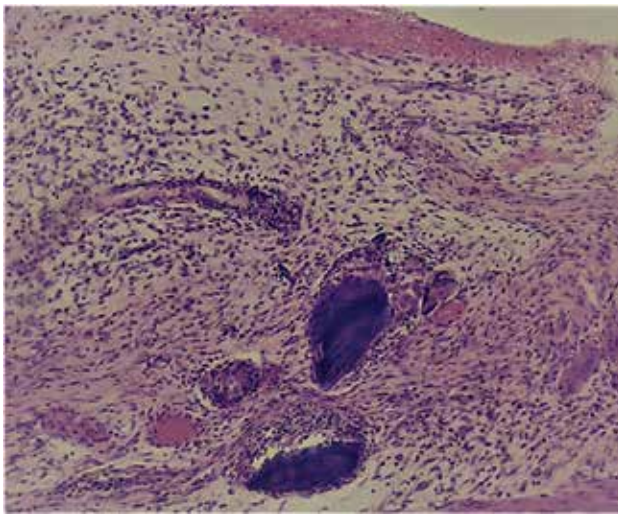


Fig. 1. Day 3. Group 4. Granulation tissue with hemodynamic disturbances, polymorphic cellular infiltration, and bone graft granules. Hematoxylin and eosin staining, $\times 100$.

Picture taken by the authors

Morphometric analysis of the modeled defect cavity revealed a predominance ($p < 0.05$) of the specific volume of blood and alternatively changed tissues in groups 1 to 3, whereas in group 4, the specific volume of connective tissue was significantly higher (Fig. 2-5). The specific volume of

blood and alternatively changed tissues decreased ($p < 0.05$) progressively from group 1 to group 4, indicating gradual clearance of the cavity from these components. The specific volume of granulation tissue increased ($p < 0.05$) from group 1 to group 2 and then decreased ($p < 0.05$) from group 2 to group 4, which reflected the maturation of granulation tissue and its transformation into connective tissue. The specific volume of connective tissue was significantly higher ($p < 0.05$) in group 4 compared to group 3.

By day 7, compared to day 3, the cavity of the perforated mandibular defect in group 4 was completely cleared of blood elements and alternatively changed tissues. The content of these components decreased in groups 1 to 3 as well, which was reflected by a significant reduction ($p < 0.05$) in the specific volume of blood and alternatively changed tissues. In group 1, the granulation tissue became more mature, and its amount in the regenerate increased, resulting in a significant increase ($p < 0.05$) in its specific volume. In groups 2 to 4, the granulation tissue showed intensive maturation and subsequent transformation into connective tissue, leading to a decrease ($p < 0.05$) in its specific volume. In group 2, connective tissue began to appear; in group 3, its specific volume increased significantly ($p < 0.05$), while in group 4 it decreased ($p < 0.05$). In all groups, predominantly in the middle and deep zones of the regenerate, osteogenic fibroreticular tissue appeared (fig. 6). In groups 2 and 4, this tissue was frequently observed in areas of osteoblast

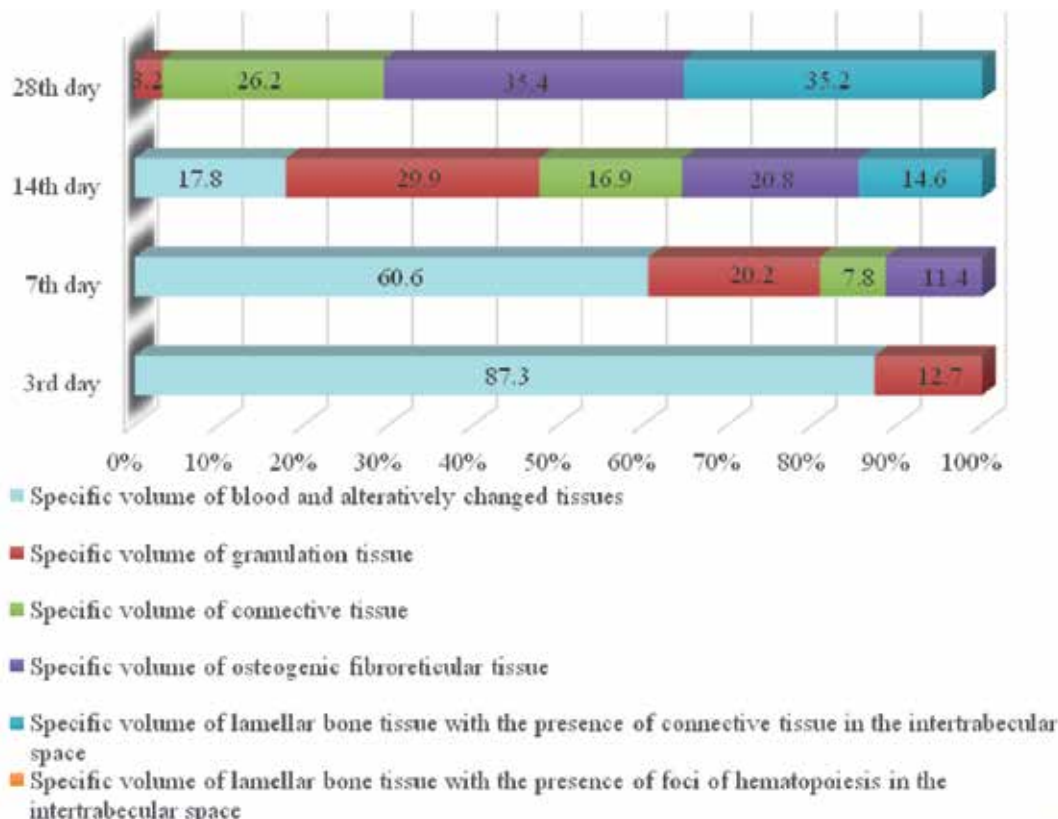


Fig. 2. Morphometric analysis results of the regenerate in group 1

Picture taken by the authors

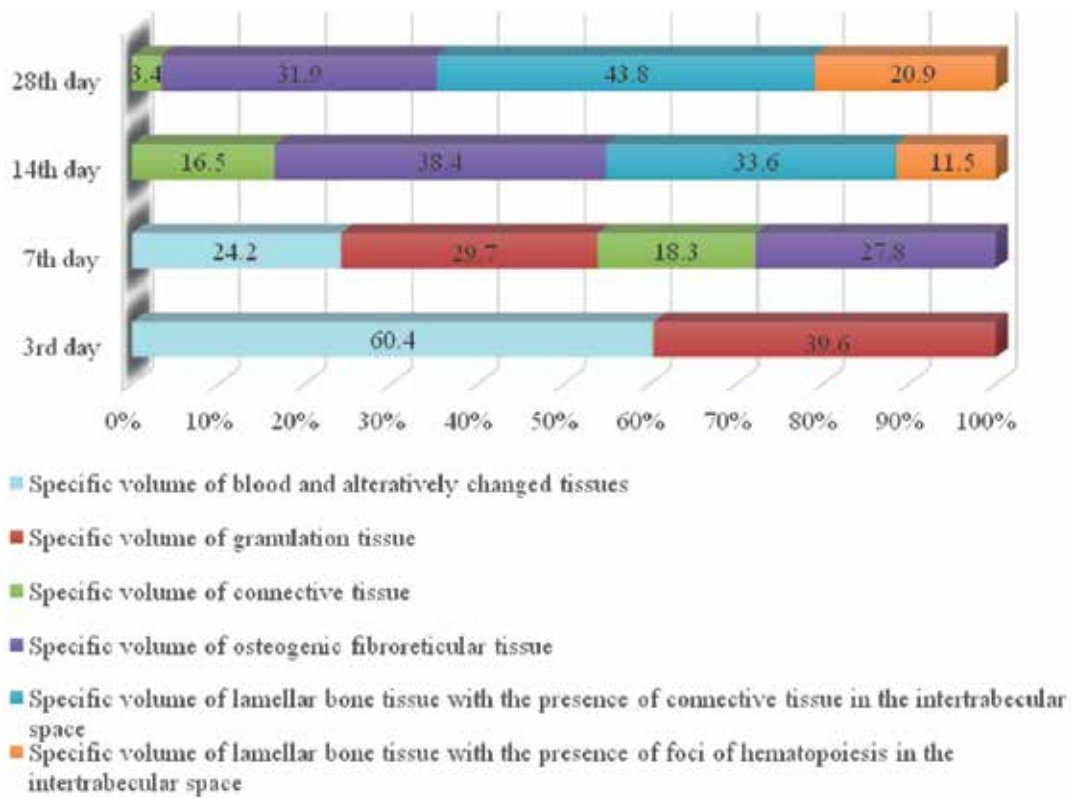


Fig. 3. Morphometric analysis results of the regenerate in group 2

Picture taken by the authors

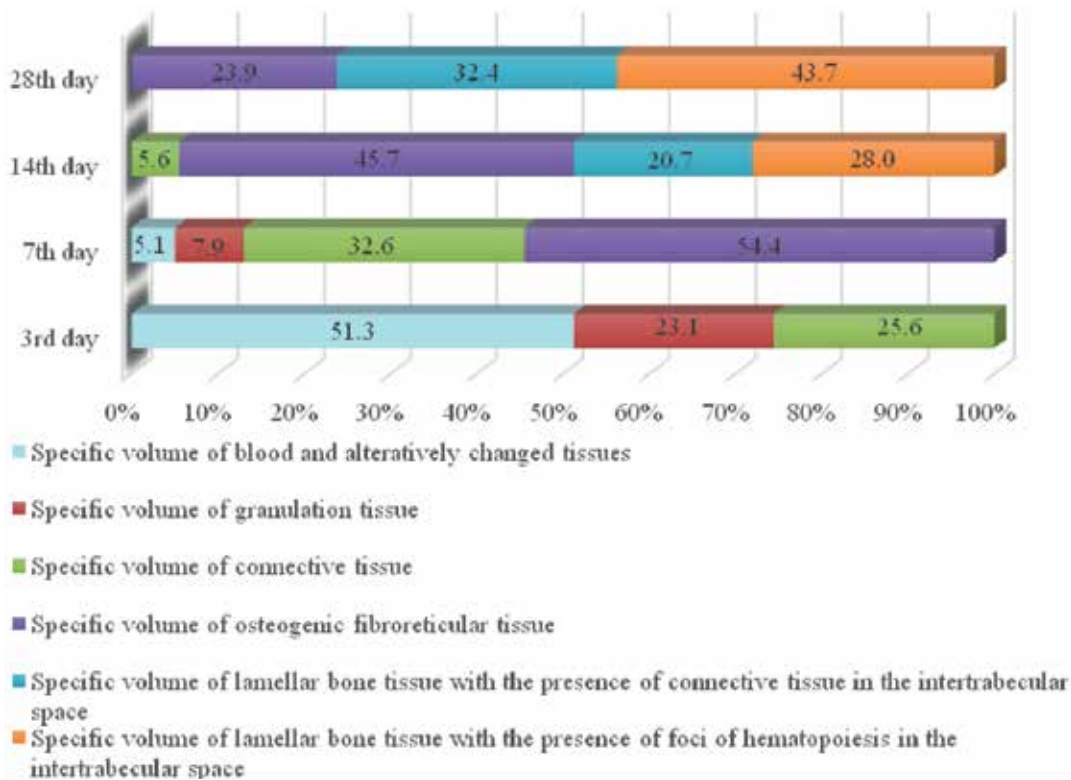


Fig. 4. Morphometric analysis results of the regenerate in group 3

Picture taken by the authors

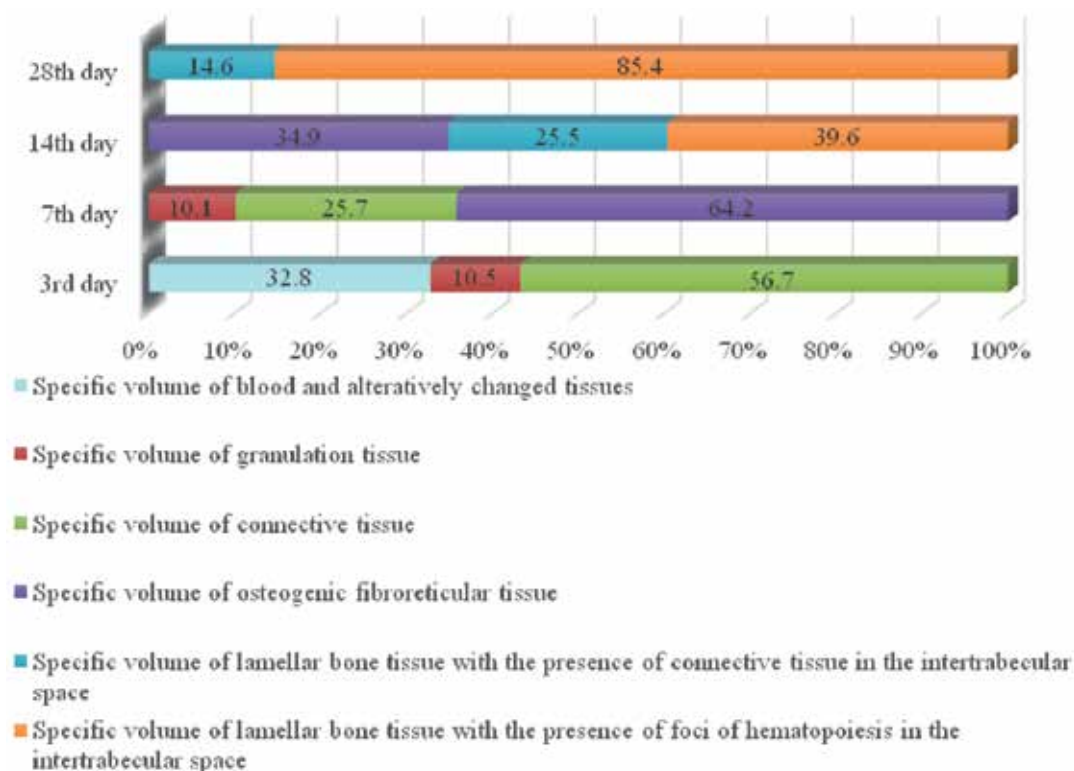


Fig. 5. Morphometric analysis results of the regenerate in group 4

Picture taken by the authors

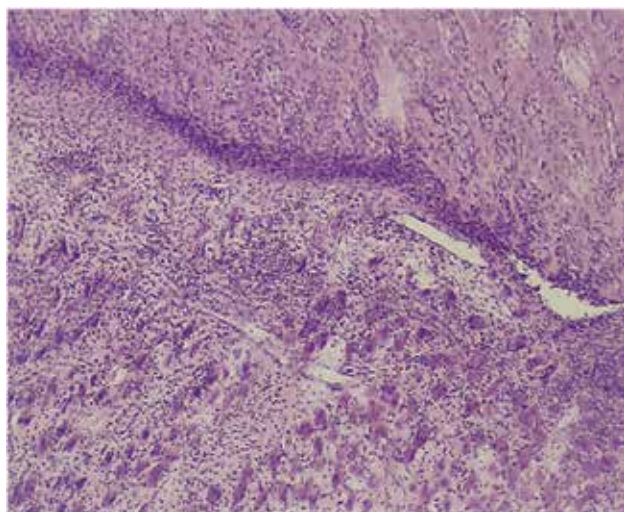


Fig. 6. Day 7. Group 4. Granulation, connective, and osteogenic fibroreticular tissues in the regenerate area. Polymorphic cellular infiltration with numerous osteoclasts observed within the granulation and connective tissues. Hematoxylin and eosin staining, $\times 100$

Picture taken by the authors

accumulation near bone graft granules embedded in the connective tissue. The number of bone graft granules remained unchanged. Hemodynamic disturbances were identified within the granulation, connective, and osteogenic fibroreticular tissues. The severity of these disturbances decreased compared to day 3 and in the direction from group 1 to group 4.

Polymorphic cellular infiltration within the granulation and connective tissues increased. In groups 1 and 2, there was an increase in the number of neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, osteoclasts, and cells of the fibroblastic lineage; osteoblasts also began to appear. In groups 3 and 4, the number of neutrophilic leukocytes, monocytes, lymphocytes, and mast cells decreased, while the number of macrophages, osteoclasts, and fibroblastic lineage cells increased; osteoblasts also emerged (fig. 6).

Intergroup analysis of the obtained morphometric parameters revealed a significant decrease ($p < 0.05$) in the specific volume of blood and alternatively changed tissues from group 1 to group 3. The specific volume of granulation tissue increased significantly ($p < 0.05$) in group 2 compared to group 1, decreased ($p < 0.05$) in group 3 compared to group 2, and showed no significant change ($p > 0.05$) in group 4 compared to group 3. The specific volume of connective tissue increased ($p < 0.05$) progressively from group 1 to group 3, but decreased significantly ($p < 0.05$) in group 4 compared to group 3. The specific volume of osteogenic fibroreticular tissue increased significantly ($p < 0.05$) from group 1 to group 4.

On day 14, compared to day 7, the rate of reparative osteogenesis increased progressively from group 1 to group 4, as evidenced by the results of overview microscopy and morphometric analysis. In group 1, residual blood and tissue debris were still present in the defect cavity, although in lesser amounts, whereas in groups 2 to 4 these elements were no longer detected. In the regenerate of

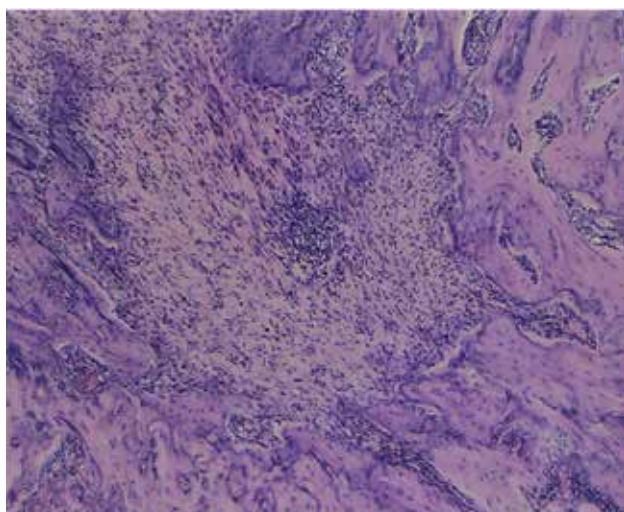


Fig. 7. Day 14. Group 1. Mature granulation tissue and connective tissue. Hematoxylin and eosin staining, $\times 100$

Picture taken by the authors

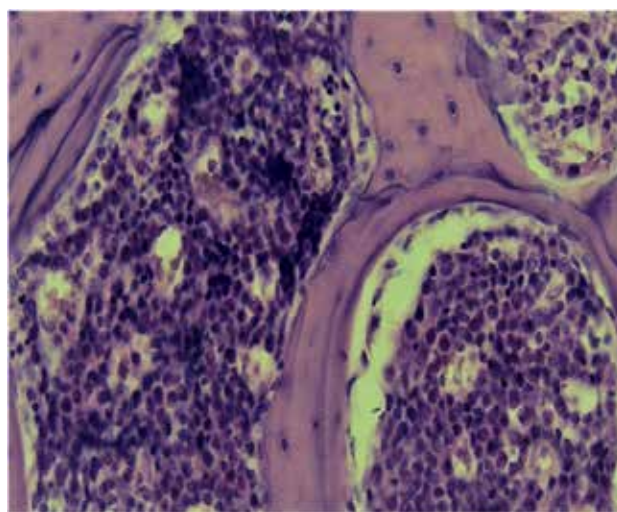


Fig. 8. Day 14. Group 4. Lamellar bone tissue with areas of hematopoiesis. Hematoxylin and eosin staining, $\times 400$

Picture taken by the authors

group 1, the specific volume of mature granulation tissue significantly increased ($p < 0.05$) (fig. 7), while this tissue type was not observed in groups 2 to 4. The specific volume of connective tissue increased significantly ($p < 0.05$) in group 1, remained unchanged ($p > 0.05$) in group 2, and decreased ($p < 0.05$) in group 3. In group 4, connective tissue was not identified in the regenerate. The specific volume of osteogenic fibroreticular tissue increased significantly ($p < 0.05$) in groups 1 and 2, while it decreased ($p < 0.05$) in groups 3 and 4.

In the regenerate of group 1, lamellar bone tissue containing connective tissue in the intertrabecular space was observed, whereas in groups 2 to 4, lamellar bone tissue was present with both connective tissue and foci of hematopoiesis within the intertrabecular space (fig. 8). Notably, in group 2, the specific volume of lamellar bone tissue containing connective tissue in the intertrabecular space predominated ($p < 0.05$), while in groups 3 and 4, the specific volume of lamellar bone tissue with hematopoietic foci in the intertrabecular space was significantly higher ($p < 0.05$).

Hemodynamic disturbances in the tissues of the regenerate area were observed only in groups 1 and 2, with a decreased severity compared to day 7. The degree of polymorphic cellular infiltration in the regenerate tissue also decreased. In groups 1 and 2, the infiltration showed a reduction in the number of neutrophilic leukocytes, monocytes, lymphocytes, and mast cells, along with an increase in the number of macrophages, osteoclasts, osteoblasts, and cells of the fibroblastic lineage. In groups 3 and 4, inflammatory cells were virtually absent from the cellular infiltration. There was an increase in the number of osteoblasts and fibroblastic lineage cells, while the number of macrophages and osteoclasts decreased.

Intergroup analysis revealed no significant change ($p > 0.05$) in the specific volume of connective tissue in group 2 compared to group 1, while a significant decrease

($p < 0.05$) was observed in group 3 compared to group 2. The specific volume of osteogenic fibroreticular tissue increased significantly ($p < 0.05$) from group 1 to group 3 and decreased ($p < 0.05$) in group 4 compared to group 3. The specific volume of lamellar bone tissue containing connective tissue in the intertrabecular space increased significantly ($p < 0.05$) in group 2 compared to group 1, decreased ($p < 0.05$) in group 3 compared to group 2, and remained unchanged ($p > 0.05$) in group 4 compared to group 3. The specific volume of lamellar bone tissue containing foci of hematopoiesis in the intertrabecular space increased significantly ($p < 0.05$) from group 2 to group 4.

On day 28 of the experiment, compared to day 14, the specific volume of mature granulation tissue in the regenerate of group 1 decreased significantly ($p < 0.05$), while the specific volumes of connective tissue, osteogenic fibroreticular tissue, and lamellar bone tissue without hematopoietic foci increased significantly ($p < 0.05$). In group 2, the specific volumes of connective and osteogenic fibroreticular tissues decreased significantly ($p < 0.05$), whereas the content of lamellar bone tissue containing both connective tissue and foci of hematopoiesis in the intertrabecular space increased significantly ($p < 0.05$). In group 3, the specific volume of osteogenic fibroreticular tissue decreased ($p < 0.05$), while the content of lamellar bone tissue with intertrabecular connective tissue and hematopoietic foci increased significantly ($p < 0.05$). In group 4, osteogenic fibroreticular tissue was not detected in the formed regenerate. The specific volume of lamellar bone tissue with intertrabecular connective tissue decreased ($p < 0.05$), whereas the specific volume of lamellar bone tissue with hematopoietic foci in the intertrabecular space increased significantly ($p < 0.05$).

DISCUSSION

The authors' comprehensive morphological analysis of experimental material demonstrated an activation of

reparative osteogenesis in the mandible in cases where the perforated defect was filled either with the synthetic bone graft «Biomim GT», containing hydroxyapatite and β -tricalcium phosphate, or with a collagen sponge containing polydeoxyribonucleotide. The therapeutic effect was more pronounced in the group treated with the collagen sponge impregnated with polydeoxyribonucleotide. However, neither of these treatment strategies led to the formation of fully mature bone regenerate by day 28 of the experiment. In contrast, the simultaneous application of the synthetic bone graft «Biomim GT» and the collagen sponge with polydeoxyribonucleotide resulted in a more active stimulation of reparative osteogenesis and contributed to the formation of a structurally complete bone regenerate by day 28.

Reparative osteogenesis is a complex, multistage process involving the participation of various cell types. Numerous researchers distinguish three phases within this process: the inflammatory phase, the reparative phase, and the remodeling phase [13]. The ultimate outcome of reparative osteogenesis is the complete restoration of bone as a functional organ [14].

In our study, from day 3 to day 28 of the experiment, the cavity of the perforated defect was progressively cleared of blood and alternatively changed tissues with varying intensity depending on the treatment method applied, and became filled with regenerate tissue. Over time, granulation tissue appeared within the regenerate, subsequently maturing and transforming into connective tissue. As the specific volume of the latter decreased, osteogenic fibroreticular tissue emerged and was gradually replaced by lamellar bone tissue containing both connective tissue and foci of hematopoiesis in the intertrabecular space.

In our view, the effectiveness of the synthetic bone graft «Biomim GT», which contains hydroxyapatite and β -tricalcium phosphate, in the treatment of mandibular bone defects is attributable to its osteoconductive properties. Specifically, osteogenic lineage cells were observed to attach to, grow on, and proliferate along the surface of the graft granules, ultimately contributing to the formation of bone tissue. The presence of β -tricalcium phosphate in the composition of the synthetic graft enhances the integration of the polymeric material with native bone tissue, thereby improving its reparative capacity [15].

The stimulation of reparative osteogenesis in cases where the perforated defect was filled with a collagen sponge containing polydeoxyribonucleotide is attributed to both the properties of the collagen scaffold itself and the biological effects of polydeoxyribonucleotide. The collagen sponge acts as a structural framework onto which osteogenic lineage cells adhere. These cells proliferate, ultimately leading to bone formation. Our findings also demonstrated that fibroblastic lineage cells attach to the collagen sponge, and these cells are known to produce the main components of connective tissue [16]. The collagen sponge also enhances the mineralization capacity of osteoblasts [17], inhibits osteoclast differentiation in mineralization formation [18].

Numerous studies have demonstrated the bone regenerative capacity of polydeoxyribonucleotide [7, 19]. Polydeoxyribonucleotide also exhibits anti-apoptotic, anti-osteoporotic, and anti-osteonecrotic effects, suppresses inflammation, enhances the morphofunctional activity of osteoblastic lineage cells, and stimulates angiogenesis [8, 9].

Thus, the aforementioned properties and biological effects of the synthetic bone graft «Biomim GT», containing hydroxyapatite and β -tricalcium phosphate, and the collagen sponge with polydeoxyribonucleotide, when used in combination, effectively stimulated reparative osteogenesis, resulting in the formation of a complete bone regenerate in the mandible of experimental animals by day 28.

CONCLUSIONS

Simultaneous filling of a bone defect in the mandible modeled in rats with the synthetic bone graft «Biomim GT», containing hydroxyapatite and β -tricalcium phosphate, and a collagen sponge with polydeoxyribonucleotide stimulates reparative osteogenesis and leads to the formation of a complete bone regenerate by day 28 of the experiment. The therapeutic effect is due to the rapid clearance of the defect cavity from blood fragments and alternatively changed tissues; active production and replacement within the regenerate of granulation, connective, and osteogenic fibroreticular tissues with the formation of lamellar bone tissue characterized by the presence of hematopoietic foci; decrease in the severity of inflammatory infiltration and hemodynamic disturbances in the tissues of the regenerate area.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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