ORIGINAL ARTICLE

CONTENTS

Reparative osteogenesis in mandible in cases of filling a bone defect with hydroxyapatite-containing osteotropic material and injecting the surrounding soft tissues with thymalin: experimental and morphological study

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ABSTRACT

Aim of the study was to identify the morphological features of reparative osteogenesis in the lower jaw bone of rats in cases of filling a bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injecting the surrounding soft tissues with thymalin.

Materials and Methods: An experiment was conducted on 48 mature rats of the WAG population weighing 160-180 grams which were divided into four groups. Group 1 included 12 rats with a simulated holey defect in the lower jaw. Group 2 included 12 rats with a simulated holey defect in the lower jaw followed by its closure with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT"). Group 3 included 12 rats with a simulated holey defect in the lower jaw with injecting the surrounding soft tissues with thymalin. Group 4 included 12 rats with a simulated holey defect in the lower jaw followed by its closure with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injecting the surrounding soft tissues with thymalin. The material for the morphological study was a fragment of the lower jaw from the area of the simulated holey defect. Histological, morphometric and statistical research methods were used.

Results: In this study, it was shown by the authors an activation of reparative osteogenesis in the lower jaw under conditions of simultaneous filling the bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injection the surrounding bone defect soft tissue with thymalin. Stimulation of reparative osteogenesis in the lower jaw of rats occurred due to rapid cleaning of the bone defect cavity from necrotic tissues and hematoma fragments; a decrease in the number of neutrophil leukocytes, an increase in the number and morphofunctional state of monocytes, macrophages, lymphocytes, cells of fibroblastic differon; balanced change (increase or decrease) in the number and morphofunctional state of bone forming osteoblasts and bone resorbing osteoclasts depending on the stage of reparative osteogenesis; activation of hematopoietic processes in lamellar bone tissue from the regenerate; activation of bone tissue mineralization processes.

Conclusions: Thymalin injection in the soft tissues surrounding the bone defect in the lower jaw, filled with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT"), significantly stimulates the process of reparative osteogenesis, which makes it possible to recommend this technique in dentistry for treatment the patients with mandible bone tissue defects.

KEY WORDS: reparative osteogenesis, mandible bone tissue defects, morphology, experiment, hydroxyapatite-containing osteotropic material, thymalin

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INTRODUCTION

The mandible is the strongest and largest bone in the face which plays a central role in function and aesthetics in the oral and maxillofacial region [1]. Mandible bone tissue defects may result from systemic (congenital abnormalities, general diseases, medications) or local (inflammation, tumor, traumatic injuries, such as accidents or dental and surgical treatments) causes [2]. These defects cause severe external deformities and dysfunction in patients due to their special anatomical position, causing facial deformities, seriously reducing their life quality [3].

Trauma is the most common cause of the lower jaw bone injury [4]. When a bone breaks or cracks, the injury is called a fracture [5]. Mandibular fractures are among the most common (60-70%) maxillofacial fractures [6] which have a multi-factorial etiology, such as road traffic accidents, accidental falls, assaults, industrial mishaps, sports injuries, firearm injuries etc. [4].

Treatment of patients with mandible bone tissue defects and reparative osteogenesis stimulation in it is an urgent issue today, despite the large number of invasive and non-invasive treatment approaches and scientific research on this topic [7]. Whilst recent

advances in surgical techniques and biomaterials have improved outcomes of the treatment of mandibular defects, situations still arise when intrinsic regeneration is not possible [8]. The mandible is more difficult to repair than other parts of the bone because of its radians, irregular shapes, dentition and oral function [3]. Treatment measures for this category of patients should be aimed at fully restoring the anatomical integrity and functions of the lower jaw [9, 10]. The latter actualizes the conduct of complex clinical and experimental studies aimed at expanding the arsenal of treatment methods and ways of stimulating reparative osteogenesis.

Our earlier morphological studies of the experimental material proved the activation of reparative osteogenesis in cases of filling a bone defect with a hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and the simultaneous application of electrical stimulation [11, 12]. A promising method of treating patients with mandibular bone defects, from our point of view, may be filling the bone defect with a hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") while simultaneously injecting the surrounding soft tissues with the immunomodulatory drugs, due to immune cells play an important role in reparative osteogenesis [13]. Thymalin can be used as such immunomodulatory drug containing a polypeptide extract of thymus.

AIM

The purpose of the study was to identify the morphological features of reparative osteogenesis in the lower jaw bone of rats in cases of filling a bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injecting the surrounding soft tissues with thymalin.

MATERIALS AND METHODS

An experiment was conducted on 48 mature rats of the WAG population weighing 160-180 grams at the experimental biological clinic of Bogomolets National Medical University. Four groups were formed (Fig. 1).

Group 1 included rats that underwent an incision of the skin, subcutaneous tissue, and superficial fascia in the left submandibular area with a length of 1-1.2 cm and skeletonized a fragment of the outer surface of the branch and body of the lower jaw under ketamine intraperitoneal anesthesia and ultracaine infiltration anesthesia. A ball-shaped drill bit for a straight tip with a diameter of 3 mm with a rotation frequency up to 1000 revolutions per minute was used to form a transcortical hole defect of the body of the lower jaw in the form of a channel, departing from the lower edge of the lower jaw upwards by 2 mm (until the feeling of the bur falling through). The wound was sutured layer by layer with polyamide after the formation of a holey defect.

Group 2 included rats that were modeled with a lower jaw defect similar to group 1. The formed defect was filled with synthetic bone graft "Biomin GT" (RAPID, Ukraine), which included hydroxyapatite and β-tricalcium phosphate. The wound was sutured layer by layer with polyamide.

Group 3 included rats that were modeled with a lower jaw defect similar to groups 1 and 2. The wound was sutured layer by layer with polyamide. Thymalin (LLC PP BIOPHARMA, Ukraine) was injected into the soft tissues around the defect for 10 days (0.01 mg/ml per 100 grams of animal weight).

Group 4 included rats that were modeled with a lower jaw defect similar to groups 1-3, which was filled with synthetic bone graft "Biomin GT" (RAPID. Ukraine). The wound was sutured layer by layer with polyamide. Thymalin (0.01 mg/ml per 100 grams of animal weight) was injected into the soft tissues around the defect for 10 days.

In groups 1-4 the animals were removed from the experiment on 3, 7, 14 and 28 days (3 animals for each experimental period).

The material for the morphological study was a fragment of the lower jaw from the area of the simulated holey defect. 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. From paraffin blocks serial sections with a thickness of 4-5 μm were made, which were stained with hematoxylin and eosin, picrofuchsin according to van Gieson.

Examination of the microslides was carried out using a laboratory microscope ZEISS Primostar 3 (Carl Zeiss, Germany) with a built-in color digital camera. Morphometry was carried out using the Labscope program. During a morphometric study, it was determined in the lamellar bone tissue of the regenerate the specific volume of bone trabeculae (%); the specific volume of intertrabecular space (%); the specific volume of intertrabecular space filled with connective tissue (%); the specific volume of intertrabecular space with foci of hematopoiesis (%).

In microslides stained with hematoxylin and eosin in the bone tissue surrounding the holey defect, the brightness coefficient was determined in the Lab color model using the computer program "Analysis of color properties of raster images" [14].

The indicators in the groups were processed statistically using the PAST program (version 4.15, Natural

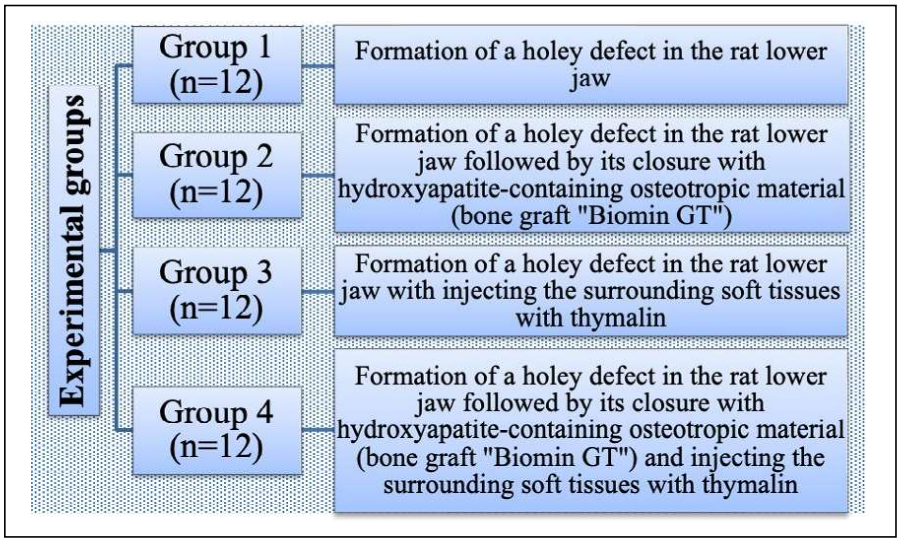

Fig. 1. Characteristics of the experimental groups.

History Museum, University of Oslo, Norway). Mean values of indicators in groups were compared using the Student's t-test and Mann-Whitney U-test. Differences were considered significant at $p<0.05$.

RESULTS

On the 3rd day of the experiment, an extensive defect was revealed in the bone tissue of the lower jaw of rats of groups 1-4, in the lumen of which, among fragments of blood, fragments of stratified squamous epithelium, muscle, connective and bone tissues with dystrophic and necrotic changes were noted. In groups 2 and 4, bone graft granules were identified among necrotic tissues and blood elements. In all groups, alteratively changed epithelial and mesenchymal tissues were diffusely infiltrated with neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, and cells of fibroblastic differon (Fig. 2). Among the polymorphic cellular infiltration, neutrophil leukocytes predominated in groups 1 and 2, and monocytes, macrophages, lymphocytes and fibroblastic cells predominated in groups 3 and 4. In groups 3 and 4, osteoclasts were also identified among the cellular elements, represented by large multinucleated cells, which were often located around alteratively changed fragments of bone tissue. In all groups, foci of immature granulation tissue were identified in the defect cavity, characterized by the presence of many full-blooded capillaries and varying densities of cellular infiltration (Fig. 2). The latter was sparsely cellular in groups 1 and 2, and densely cellular in groups 3 and 4. Granulation tissue in groups 2 and 4 was often localized around bone graft granules.

In the bone tissue surrounding the defect, the edges had unclear outlines with signs of resorption. The latter changes were due to the activation of the morphofunctional state of osteoclasts, which was more pronounced in groups 3 and 4 (Fig. 2). Moderate or pronounced alterative changes were also identified in this tissue, which were manifested by uneven staining of the structures with hematoxylin and eosin. A morphometric study determined the brightness coefficient in bone tissue, which did not differ ($p>0.05$) in groups 1-4 (Table 1). In the periosteum, pronounced dystrophic-necrotic changes, hemodynamic disturbances represented by edema, vascular congestion and hemorrhages were noted. In these tissues, polymorphic cellular infiltration was represented by neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, and cells of fibroblastic differon. Polymorphic cellular infiltration was characterized in groups 1 and 2 by a predominance of neutrophilic leukocytes, and in groups 3 and 4 – monocytes, macrophages, lymphocytes and fibroblastic cells.

On the 7th day of the experiment, compared to the 3rd day, in the lumen of the bone defect the remains of a blood clot, represented by masses of fibrin and hemolyzed erythrocytes with an erased pattern, were noted; the specific volume of alteratively changed tissues decreased. These changes were more pronounced in groups 3 and 4 compared to groups 1 and 2. Alternatively changed tissues, as on the 3rd day of the experiment, were diffusely infiltrated with neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, cells of fibroblastic differon, among which neutrophilic leukocytes predominated in groups 1 and 2, and monocytes, lymphocytes, macrophages, cells of fibroblastic differon – in groups 3 and 4. On the 7th day of the experiment, compared to the 3rd day, in all groups, among the detected infiltration, the number of monocytes, lymphocytes, macrophages, and fibroblastic cells increased. Mature granulation, connective and osteogenic fibroreticular tissues were also detected in the lumen of the bone defect.

Table 1. Average values of the brightness coefficient in the bone tissue surrounding the holey defect in groups 1-4

Group	Day of the experiment			
	3	7	14	28
1 holey defect	0.66±0.009	0.66±0.013	0.63±0.010 [4]	0.59±0.007 [4]
2 holey defect+bone graft "Biomin GT"	0.67±0.009	0.66±0.001	0.64±0.008 [4]	0.59±0.008 [4]
3 holey defect+thymalin	0.66±0.009	0.62±0.015 [1,2,4]	0.58±0.007 [1,2,4]	0.53±0.012 [1,2,4]
4 holey defect+bone graft "Biomin GT"+ thymalin	0.65±0.010	0.61±0.015 [1,2,4]	0.56±0.010 [1,2,4]	0.53±0.008 [1,2,4]

Note: [1] – significance of differences compared to the indicator of group 1; [2] – significance of differences compared to the indicator of group 2; [3] – significance of differences compared to the indicator of group 3; [4] – significance of differences compared to the previous period of the experiment.

In group 3 and, especially, in group 4, compared with groups 1 and 2, there was a higher content of osteogenic fibroreticular tissue. The latter was determined in areas of osteoblasts accumulation in the connective tissue in groups 1-4, and in groups 2-4 also around the bone graft. In single fields of view in group 4, isolated, weakly mineralized bone beams were visible in the connective tissue (Fig. 3).

Alterative changes of varying degrees of severity were identified in the bone tissue that bordered the defect cavity (moderately expressed in groups 3 and 4, pronounced in groups 1 and 2). The brightness coefficient in bone tissue in groups 3 and 4 had a significantly ($p<0.05$) lower value compared to groups 1 and 2, which indicated a greater degree of mineralization of bone tissue (Table 1). The brightness coefficient did not change ($p>0.05$) in groups 1 and 2, but decreased ($p<0.05$) in groups 3 and 4 on the 7th day compared to the 3rd day.

Predominantly in groups 3 and 4 compared to groups 1 and 2, the periosteal and endosteal surfaces of the bone tissue bordering the defect were characterized by a high density of osteogenic cells and their increased proliferative potential with the formation of osteogenic fibroreticular tissue (Fig. 4). The layers of the latter anastomosed with each other, grew towards the defect and filled its lumen.

On the 14th day of the experiment, the regenerate filling the lumen of the bone defect was represented in all groups by granulation tissue of varying degrees of maturity, connective, osteogenic fibroreticular and lamellar bone tissues. Among these tissues in the regenerate, granulation and connective tissues predominated in group 1, osteogenic fibroreticular and lamellar bone tissues predominated in group 2, and lamellar bone tissue predominated in group 3 and, especially, in group 4. In groups 2 and 4, active osteogenesis processes were observed around the bone graft granules, the number of which, compared to day 7, did not change. In some of the visual fields, a connective tissue capsule was formed around the graft granules (Fig. 5). In the capsule, as well as in the tissues surrounding the capsule, cellular infiltration was revealed, represented by lymphocytes, monocytes, macrophages, fibroblastic cells.

In groups 1-4, in lamellar bone tissue, bone trabeculae were characterized by heterogeneous staining with hematoxylin and eosin, which indicated varying degrees of mineralization. The bone trabeculae of the regenerate were stained less intensely with hematoxylin and eosin compared to bone tissue, which was located at a distance from the defect. The decrease in the intensity of staining of the bone trabeculae of the regenerate was more pronounced in group 1 compared to groups 2, 3 and, especially, group 4.

During morphometry, it was noted that in all groups in the lamellar bone tissue of the regenerate, the specific volume of bone trabeculae prevailed ($p<0.05$) compared to the specific volume of the intertrabecular space (Table 2). During survey microscopy, in the intertrabecular spaces, connective tissue with full-blooded vessels or foci of hematopoiesis were identified. It was noted that in all groups the specific volume of intertrabecular spaces filled with connective tissue prevailed ($p<0.05$) compared to the specific volume of intertrabecular spaces with foci of hematopoiesis.

During the analyzing of the obtained indicators, it was noted that the specific volume of bone trabeculae significantly ($p<0.05$) increased from group 1 to group 4, and the specific volume of intertrabecular space decreased significantly ($p<0.05$). The specific volume of intertrabecular space filled with connective tissue and the specific volume of intertrabecular space with the areas of hematopoiesis did not differ significantly ($p>0.05$) in group 1 compared to group 2, in group 3 compared to group 4. However, in groups 3 and 4, compared with groups 1 and 2, the specific volume of intertrabecular space filled with connective tissue and the specific volume of intertrabecular space with the ar-

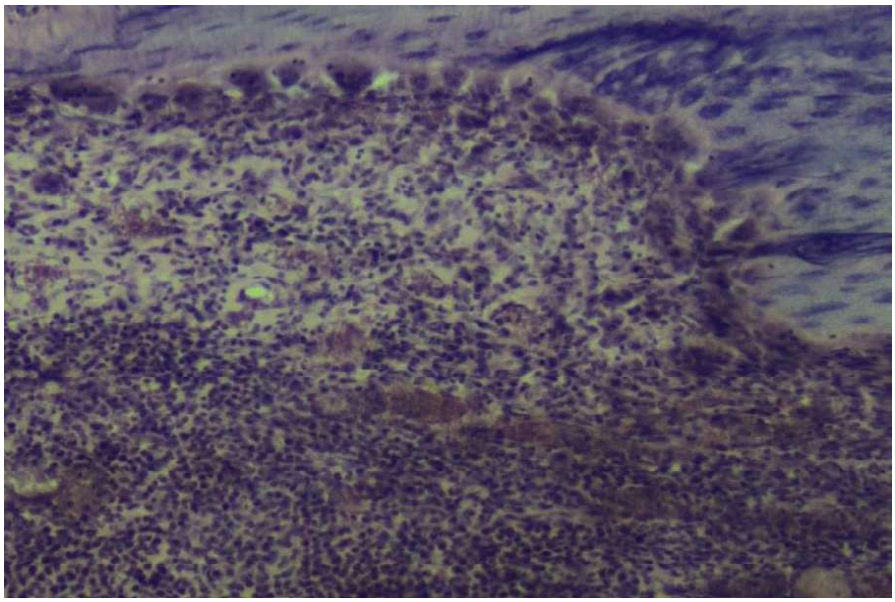

Fig. 2. Group 3. Polymorphic cellular infiltration and immature granulation tissue in the lumen of the bone defect. Resorption by osteoclasts of adjacent to the bone tissue defect. Hematoxylin and eosin staining, ×400.

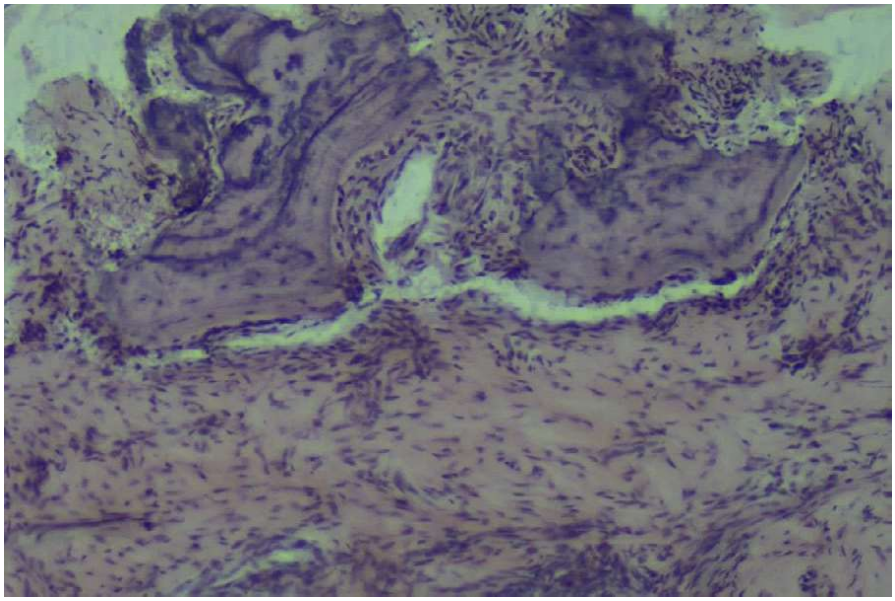

Fig. 3. Group 4. Single, isolated from each other, weakly mineralized bone beams in the connective tissue fields. Hematoxylin and eosin staining, ×400.

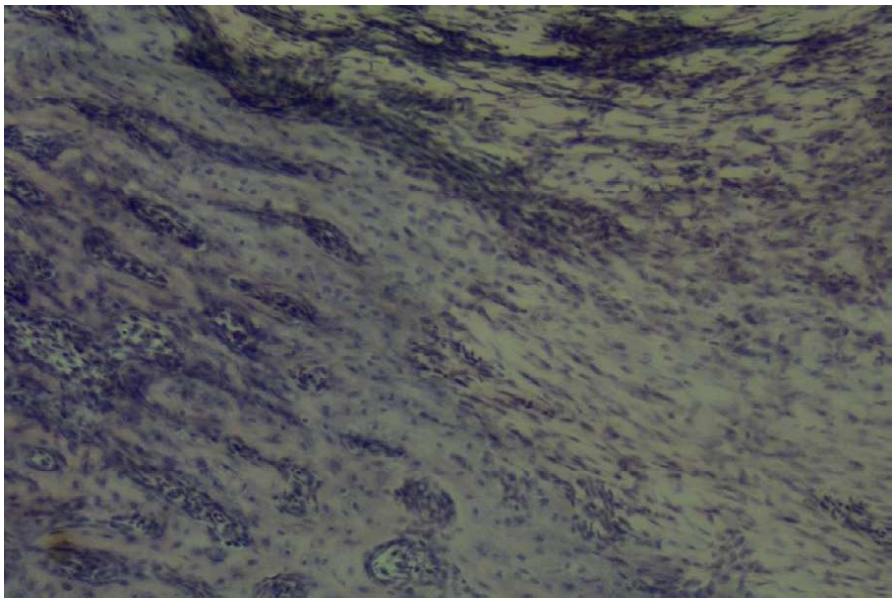

Fig. 4. Group 3. Layers of osteogenic fibroreticular tissue anastomose with each other and fill the lumen of the bone defect. Hematoxylin and eosin staining, ×100.

Table 2. Morphometric study of the lamellar bone tissue from regenerate in groups 1-4

Group	Morphometric indicator	Day of the experiment	
		14	28
1 holey defect	Specific volume of bone trabeculae (%)	54.3±2.05	64.8±2.16
	Specific volume of intertrabecular space (%)	45.8±2.05[1]	35.2±2.16[1]
	Specific volume of intertrabecular space filled with connective tissue (%)	87.1±2.98	75.8±3.41
	Specific volume of intertrabecular space with hematopoiesis foci (%)	12.9±2.98[2]	24.2±3.41[2]
2 holey defect+bone graft "Biomin GT"	Specific volume of bone trabeculae (%)	60.4±2.35[3]	70.5±1.79[3]
	Specific volume of intertrabecular space (%)	39.6±2.35[1,3]	29.5±1.79[1,3]
	Specific volume of intertrabecular space filled with connective tissue (%)	85.4±2.98	74.7±3.12
	Specific volume of intertrabecular space with hematopoiesis foci (%)	14.6±2.98[2]	25.3±3.12[2]
3 holey defect+thymalin	Specific volume of bone trabeculae (%)	66.3±2.51[3,4]	75.8±2.55[3,4]
	Specific volume of intertrabecular space (%)	33.7±2.51[1,3,4]	24.2±2.55[1,3,4]
	Specific volume of intertrabecular space filled with connective tissue (%)	64.9±2.48[3,4]	38.9±2.14[3,4]
	Specific volume of intertrabecular space with hematopoiesis foci (%)	35.1±2.48[2,3,4]	61.1±2.14[2,3,4]
4 holey defect+bone graft "Biomin GT"+ thymalin	Specific volume of bone trabeculae (%)	72.2±2.20[3,4,5]	81.3±2.63[3,4,5]
	Specific volume of intertrabecular space (%)	27.8±2.20[1,3,4,5]	18.7±2.63[1,3,4,5]
	Specific volume of intertrabecular space filled with connective tissue (%)	66.7±2.33[3,4]	37.1±1.99[3,4]
	Specific volume of intertrabecular space with hematopoiesis foci (%)	33.3±2.33[2,3,4]	62.9±1.99[2,3,4]

Note: [1] – significance of differences compared to the specific volume of bone trabeculae; [2] – significance of differences compared to the specific volume of intertrabecular space filled with connective tissue; [3] – significance of differences compared to the indicator of group 1; [4] – significance of differences compared to group 2; [5] – significance of differences compared to the indicator of group 3.

eas of hematopoiesis took on, respectively, significantly ($p<0.05$) smaller and larger values. The morphometric study showed that in group 3 and, especially, in group 4, pronounced processes of reparative osteogenesis and hematopoiesis were observed in comparison with groups 1 and 2.

In the bone tissue that bordered the defect cavity, an active bone formation process was revealed, as evidenced by a pronounced increase in the proliferative potential of osteogenic cells located on the periosteal and endosteal surfaces. These processes were maximally expressed in group 3 and, especially, in group 4 and less pronounced in groups 1 and 2. The brightness coefficient in bone tissue in groups 3 and 4 had a significantly ($p<0.05$) lower value compared to groups 1 and 2 (Table 1). The brightness coefficient on day 14 compared to day 7 significantly ($p<0.05$) decreased in all groups.

On the 28th day of the experiment, the regenerate was represented by connective, osteogenic fibroreticular and lamellar bone tissues. In the direction from group 1 to group 4, the volume of lamellar bone tissue increased (Fig. 6), which indicated an increase in the processes of bone formation. In groups 2 and 4, the number of bone graft granules did not change compared to day 14. The bone beams in lamellar bone tissue in all groups did not have an ordered spatial arrangement and were unevenly stained with hematoxylin and eosin.

In groups 1-4, lamellar bone tissue during a morphometric study was characterized ($p<0.05$) by a predominance of the specific volume of bone trabeculae compared to the specific volume of the intertrabecular space (Table 2). In groups 1 and 2, the specific volume of the intertrabecular space filled with connective tissue was significantly ($p<0.05$) larger compared to the specific volume of the intertrabecular space with areas of hematopoiesis, however, in groups 3 and 4, the specific volume of the intertrabecular space with areas of hematopoiesis was significant ($p<0.05$) greater value compared to the specific volume of the intertrabecular space filled with connective tissue.

The data from the morphometric study indicated pronounced processes of reparative osteogenesis and hematopoiesis in group 3 and, especially, in group 4 compared to groups 1 and 2.

In the bone tissue that bordered the defect filled with regenerate, the brightness coefficient in groups 3 and 4 took on a significantly lower value (Table I) compared to groups 1 and 2. On the 28th day of the experiment, compared with 14 days, the brightness coefficient decreased in all groups (Table I).

DISCUSSION

Our previous studies and the results of numerous studies of various scientists have shown the high efficiency of

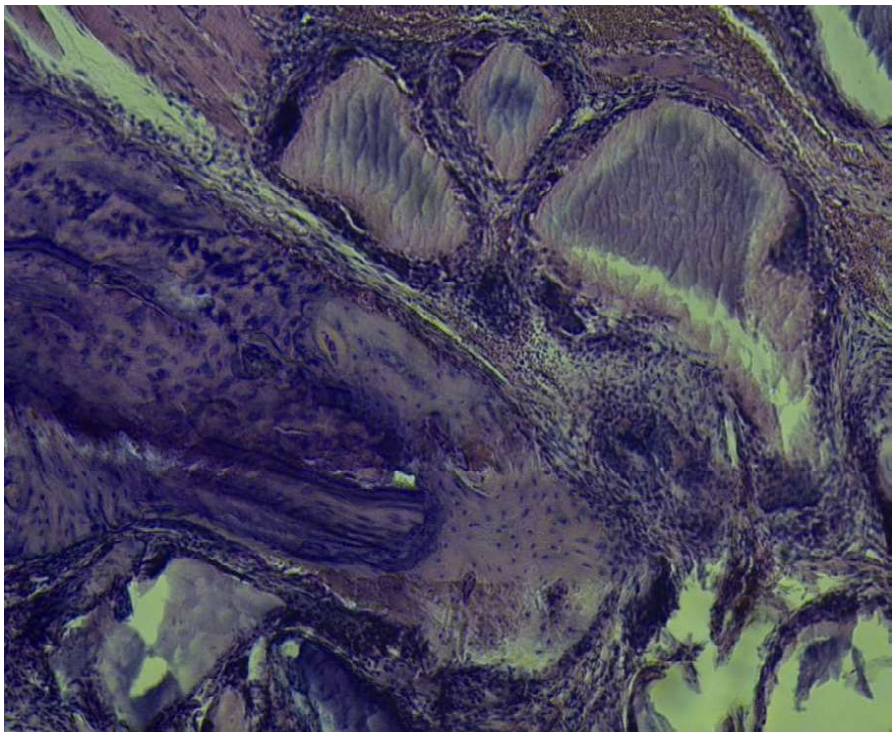

Fig. 5. Group 2. Connective tissue capsule with polymorphic cellular infiltration around the bone graft granule. Hematoxylin and eosin staining, ×400.

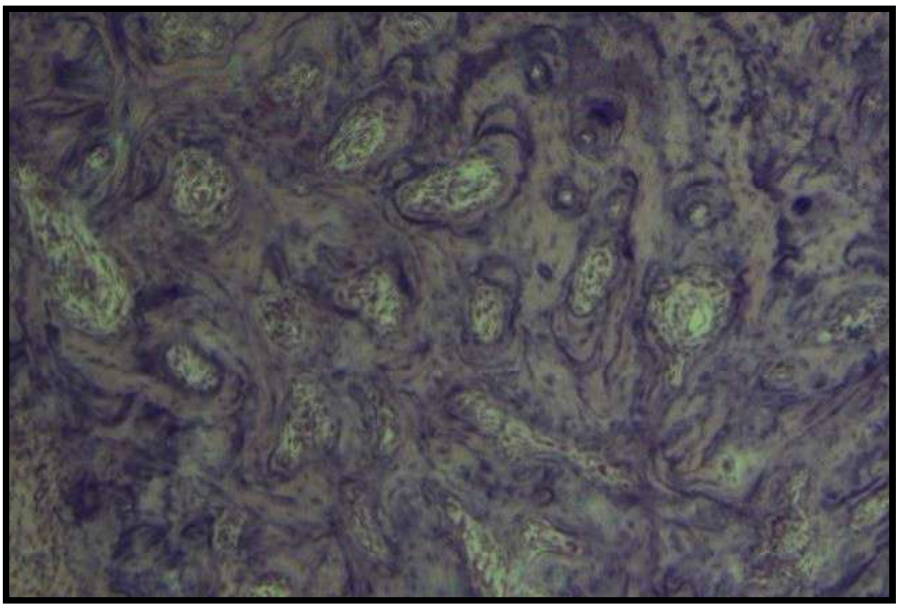

Fig. 6. Group 4. Lamellar bone tissue from the regenerate. Hematoxylin and eosin staining, ×100.

using of various osteotropic materials based on hydroxyapatite to replace the bone defects in the lower jaw [11, 15]. In this study, the authors were the first to show a more pronounced activation of reparative osteogenesis in the lower jaw under conditions of simultaneous filling the bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injection the surrounding bone defect soft tissue with thymalin.

Bone is considered an osteoimmune system which is based on cooperatively acting bone and immune cells [16]. Dysfunctions of the immune system lead to disturbances in various mechanisms of reparative osteogenesis [17, 18]. Currently, increasing evidence indicates that regulating the immune microenvironment is a promising therapeutic target to promote bone tissue regeneration [19]. We used thymalin as a regulator of local immune reactions in the area of the bone defect.

Thymalin is a polypeptide complex isolated from the thymus which regulates the number and ratio of T- and B-lymphocytes and their subpopulations, stimulates the cellular immunity reactions, enhances the phagocytosis, stimulates the processes of regeneration and hematopoiesis, and improves the processes of cellular metabolism [20].

Our study showed that the injection of thymalin into the soft tissues surrounding the bone defect, which was filled with hydroxyapatite-containing osteotropic

material (bone graft "Biomin GT"), led to rapid cleaning of the bone defect cavity from necrotic tissues and hematoma fragments; a decrease in the number of neutrophil leukocytes, an increase in the number and morphofunctional state of monocytes, macrophages, lymphocytes, cells of fibroblastic differon; balanced change (increase or decrease) in the number and morphofunctional state of bone forming osteoblasts and bone resorbing osteoclasts depending on the stage of reparative osteogenesis; activation of hematopoietic processes in lamellar bone tissue from the regenerate; activation of bone tissue mineralization processes.

CONCLUSIONS

Thymalin injection in the soft tissues surrounding the bone defect in the lower jaw, filled with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT"), significantly stimulates the process of reparative osteogenesis, which makes it possible to recommend this technique in dentistry for treatment the patients with mandible bone tissue defects.

Stimulation of reparative osteogenesis in the lower jaw of rats occurs due to the acceleration of the clearance of the bone defect cavity from necrotic tissues and hematoma fragments; reducing the number of neutrophil leukocytes, increasing the number and morphofunctional state of monocytes, macrophages, lymphocytes, cells of fibroblastic differon; balanced change (increase or decrease) in the number and morphofunctional state of bone forming osteoblasts and bone resorbing osteoclasts depending on the stage of reparative osteogenesis; activation of hematopoietic processes in lamellar bone tissue from the regenerate; activation of bone tissue mineralization processes.

REFERENCES

1. Kyriakidou E, O'Connor N, Malden NJ, Lopes VR. Bone defects of the jaws: moving from reconstruction to regeneration. Dental Update. 2014;41(7):613-622.
2. Wu V, Helder MN, Bravenboer N, Ten Bruggenkate CM, Jin J, Klein-Nulend J, Schulten EAJM. Bone Tissue Regeneration in the Oral and Maxillofacial Region: A Review on the Application of Stem Cells and New Strategies to Improve Vascularization. Stem Cells Int. 2019;2019:6279721. doi: 10.1155/2019/6279721. DOI
3. Li Y, Li D, Tang Z, Wang D, Yang Z, Liu Y. Current global research on mandibular defect: A bibliometric analysis from 2001 to 2021. Front Bioeng Biotechnol. 2023;11:1061567. doi: 10.3389/fbioe.2023.1061567. DOI
4. Khan TU, Rahat S, Khan ZA, Shahid L, Banouri SS, Muhammad N. Etiology and pattern of maxillofacial trauma. PLoS One. 2022;17(9):e0275515. doi: 10.1371/journal.pone.0275515. DOI
5. Ferneini EM. Mandibular Fractures. J Oral Maxillofac Surg. 2021;79(12):2603-2605. doi: 10.1016/j.joms.2021.08.264. DOI
6. Nardi C, Vignoli C, Pietragalla M, Tonelli P, Calistri L, Franchi L, Preda L, Colagrande S. Imaging of mandibular fractures: a pictorial review. Insights Imaging. 2020;11(1):30. doi: 10.1186/s13244-020-0837-0. DOI
7. Xue N, Ding X, Huang R, Jiang R, Huang H, Pan X, Min W, Chen J, Duan JA, Liu P, Wang Y. Bone Tissue Engineering in the Treatment of Bone Defects. Pharmaceuticals (Basel). 2022;15(7):879. doi: 10.3390/ph15070879. DOI
8. Basyuni S, Ferro A, Santhanam V, Birch M, McCaskie A. Systematic scoping review of mandibular bone tissue engineering. Br J Oral Maxillofac Surg. 2020;58(6):632-642. doi: 10.1016/j.bjoms.2020.03.016. DOI
9. Lykhytskyi OO. Modern views on etiopathogenesis of traumatic injuries of the lower jaw against the background of osteoporosis and the use of drugs for correction of the processes of reparative osteogenesis. Reports of Vinnytsia National Medical University. 2019; 23(2): 309-315. doi:10.31393/reports-vnmedical-2019-23(2)-24. DOI
10. Sverzut CE, Lucas MA, Sverzut AT, Trivellato AE, Beloti MM, Rosa AL, de Oliveira PT. Bone repair in mandibular body osteotomy after using 2.0 miniplate system – histological and histometric analysis in dogs. Int J Exp Pathol. 2008;89(2):91-97. doi: 10.1111/j.1365-2613.2007.00569.x. DOI
11. Huseynov AN, Malanchuk VA, Myroshnychenko MS, Zaytseva OV. Experimental and morphological assessment of the influence of hydroxyapatite-containing osteotropic material and electrical stimulation on reparative osteogenesis of the lower jaw. Pol Merkur Lekarski. 2023;51(4):358-366. doi: 10.36740/Merkur202304110. DOI
12. Huseynov AN, Malanchuk VA, Myroshnychenko MS, Markovska OV, Sukharieva LP, Kuznetsova MO. Morphological characteristics of reparative osteogenesis in the rats lower jaw under the conditions of using electrical stimulation. Pol Merkur Lekarski. 2023;51(6):592-597. doi: 10.36740/Merkur202306102. DOI
13. Tabanez AP, de Campos Soriani Azevedo M, Melchiades JL, Fonseca AC, Francisconi CF, Colavite PM, Biguetti CC, de Oliveira Rodini Pegoraro C, Trombone APF, Garlet GP. FTY720 administration results in a M2 associated immunoregulatory effect that positively influences the outcome of alveolar bone repair outcome in mice. Bone. 2022;163:116506. doi: 10.1016/j.bone.2022.116506. DOI
14. Ivanova M, Myroshnychenko M, Khara G, Arseniev O, Olkhovsky V, Grygorian E, Fedulenkova Y, Kozlov S. Analysis of color properties of raster images of histological microspecimens: own research experience. Med. perspekt. 2022;27(1):9-15.

15. Verma R, Mishra SR, Gadore V, Ahmaruzzaman M. Hydroxyapatite-based composites: Excellent materials for environmental remediation and biomedical applications. Adv Colloid Interface Sci. 2023;315:102890. doi: 10.1016/j.cis.2023.102890. DOI
16. Ehnert S, Relja B, Schmidt-Bleek K, Fischer V, Ignatius A, Linnemann C, Rinderknecht H, Huber-Lang M, Kalbitz M, Histing T, Nussler AK. Effects of immune cells on mesenchymal stem cells during fracture healing. World J Stem Cells. 2021;13(11):1667-1695. doi: 10.4252/wjsc.v13.i11.1667. DOI
17. El-Jawhari JJ, Jones E, Giannoudis PV. The roles of immune cells in bone healing; what we know, do not know and future perspectives. Injury. 2016;47(11):2399-2406. doi: 10.1016/j.injury.2016.10.008. DOI
18. Ono T, Takayanagi H. Osteoimmunology in Bone Fracture Healing. Curr Osteoporos Rep. 2017;15(4):367-375. doi: 10.1007/s11914-017-0381-0. DOI
19. Yang N, Liu Y. The Role of the Immune Microenvironment in Bone Regeneration. Int J Med Sci. 2021;18(16):3697-3707. doi: 10.7150/ijms.61080. DOI
20. Khavinson VK, Linkova NS, Kvetnoy IM, Polyakova VO, Drobintseva AO, Kvetnaia TV, Ivko OM. Thymalin: Activation of Differentiation of Human Hematopoietic Stem Cells. Bull Exp Biol Med. 2020;170(1):118-122. doi: 10.1007/s10517-020-05016-z. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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