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ORIGINAL ARTICLE

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MORPHOLOGICAL CHARACTERISTICS OF REPARATIVE OSTEOGENESIS IN THE RATS LOWER JAW UNDER THE CONDITIONS OF USING ELECTRICAL STIMULATION

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ABSTRACT

Aim: The purpose of the study was to identify the morphological features of reparative osteogenesis in the rats lower jaw under the conditions of using electrical stimulation.

Materials and Methods: An experiment was conducted on 24 mature male rats of the WAG population. Two groups were formed. Group 1 included 12 rats that were modeled with a perforated defect of the lower jaw body. Group 2 included 12 animals that were modeled with a perforated defect similar to group 1. In animals, a microdevice for electrical action was implanted subcutaneously in the neck area on the side of the simulated bone defect (a temporary Videx AG 4 battery; a constant sinusoidal electric current of an unchanging nature 1 milliampere, frequency 30 W). The negative electrode connected to the negative pole of the battery was in contact with the bone defect. The battery and electrode were insulated with plastic heat shrink material. Morphological and statistical methods were used.

Results: The positive effect of electrical stimulation on reparative osteogenesis was due to a decrease in the severity of hemodynamic disorders, activation of angiogenesis in granulation tissue, which was one of the components of the regenerate that filled the bone defect, matured and turned into connective tissue; stimulation of the proliferative potential of fibroblastic cells and cells with osteoblastic activity in granulation tissue; increasing the proliferative potential of osteoblastic elements of bone tissue bordering the cavity; stimulation of macrophage cells and processes of cleansing the bone cavity from fragments of a blood clot and alteratively changed tissues; formation of clusters of adipocytes in the loci of connective and granulation tissue of the regenerate; the process of metaplasia of connective tissue into bone tissue; an increase of the foci of hematopoiesis in the intertrabecular spaces of lamellar bone tissue.

Conclusions: A comprehensive clinical and experimental study conducted by the authors proved that electrical stimulation activates the reparative osteogenesis in the lower jaw, which occurs through direct osteogenesis and does not finish on the 28th day of the experiment.

KEY WORDS: electrical stimulation, rats, morphology, reparative osteogenesis, lower jaw

INTRODUCTION

Trauma is the most common cause of maxillofacial injuries. The epidemiology of maxillofacial fractures varies according to geographical areas and socio-economic factors [1]. Maxillofacial fractures have a multi-factorial etiology (road traffic accidents, accidental falls, assaults, industrial mishaps, sports injuries, firearm injuries etc.) [2]. Mandibular fractures are the most common fractures of facial skeleton. Fractures of the mandible account for 36% to 59% of all maxillofacial fractures [3, 4].

Treatment of patients with mandibular fractures is a pressing issue of medical and social importance. The main goal of treatment for this category of patients is restoration of the anatomical integrity of the lower jaw. Known surgical methods of treatment do not allow for complete high-quality reposition, fixation of bone fragments, and entail the development of posttraumatic and postoperative complications [5, 6]. Recent facts indicate the need, together with the treatment, to use methods of stimulating reparative osteogenesis, which would lead to rapid and high-quality restoration of the bone tissue of the lower jaw. Today, biological and physical methods for stimulating reparative osteogenesis are known [7]. One of the physical and promising methods may be the use of electrical stimulation.

AIM

The purpose of the study was to identify the morphological features of reparative osteogenesis in the rats lower jaw under the conditions of using electrical stimulation.

MATERIALS AND METHODS

An experiment was conducted on 24 mature male rats of the WAG population. Two groups were formed.

Group 1 included 12 rats that were modeled with a perforated defect of the lower jaw body. Anesthetized rats underwent a 1.0-1.2 cm long incision of the skin, subcutaneous tissue, and superficial fascia in the left submandibular area. A fragment of the outer surface of the branch and body of the lower jaw was skeletonized. With a ball-shaped drill and a straight tip with a diameter of 3.0 mm, a transcortical perforated defect of the body of the lower jaw was formed in the form of a channel, departing from the lower edge of the jaw upwards by 2 mm. The wound was sutured in layers with vicryl.

Group 2 included 12 animals that were modeled with a perforated defect similar to group 1. In animals, a microdevice for electrical action was implanted subcutaneously in the neck area on the side of the simulated bone defect (a temporary Videx AG 4 battery; a constant sinusoidal electric current of an unchanging nature 1 milliampere, frequency 30 W). The negative electrode connected to the negative pole of the battery was in contact with the bone defect. The battery and electrode were insulated with plastic heat shrink material.

In groups 1 and 2 the animals were removed from the experiment on 3, 7, 14 and 28 days (3 animals for each experimental period).

The study material was a fragment of the body of the lower jaw from the zone of the perforated defect modeling. The material was fixed in a 10% solution of neutral formalin (pH 7.4) for 24-48 hours, decalcified, 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 which the specific volumes of the fibrous, cellular and vascular components of granulation tissue were calculated at different experimental periods.

The indicators in the groups were processed statistically using the Statistica 10.0 program. Mean values of indicators in groups were compared using the non-parametric Mann-Whitney U-test. Differences were considered significant at $p<0.05$.

RESULTS

During survey microscopy on the 3rd day of the experiment, a bone defect was discovered in the lower jaw of rats of groups 1 and 2, passing through the entire thickness of the jaw. The defect cavity in both groups was filled with a blood clot; fragments of the epithelial layer, muscle, connective and bone tissues with dystrophic and necrotic changes, diffuse infiltration of neutrophilic leukocytes, macrophages, lymphocytes and histiocytes.

In group 2, compared to group 1, in the bone defect cavity there were significantly fewer blood clot fragments and alteratively changed tissues, and in the latter, diffuse cellular infiltration was characterized by a lower content of neutrophilic leukocytes and a larger number of the cells of macrophage line. Small loci of granulation tissue were also found in the bone defect cavity. The latter in group 1 was visualized at the edges of the bone defect, and in group 2 – at the edges and central part.

In groups 1 and 2, the granulation tissue was characterized by the presence of fibrous (specific volume in group 1 – (23.5±0.55)%, in group 2 – (34.3±0.94)%), vascular (specific volume in group 1 – (11.7±0.60)%, in group 2 – (21.5±0.67)%) and cellular (specific volume in group 1 – (64.8±0, 76)%, in group 2 – (44.2±1.31)%) components, among which the latter prevailed, which is a characteristic feature of immature granulation tissue (Fig. 1a, 1b).

In both groups, the fibrous component of the granulation tissue was characterized by the presence of thin branched connective tissue fibers. The cellular component was represented by neutrophilic leukocytes, macrophages, lymphocytes, histiocytes, fibroblastic differon cells. The latter in group 2 compared to group 1 was characterized by a lower content of neutrophilic leukocytes and a greater number of macrophages and cells of the fibroblastic series (Fig. 1a, 1b).

The vascular component was represented by vessels of different shapes and sizes, and in group 2 compared to group 1 the diameter of the vessels was significantly smaller. In group 1, granulation tissue was characterized by severe hemodynamic disturbances, manifested by dilation and congestion of blood vessels, edematous changes in the vascular walls, perivascular edema, formation of thrombi in the cavity of some vessels, small focal hemorrhages (Fig. 1a).

A comparative intergroup analysis of the obtained morphometric parameters showed a more pronounced degree of maturity of granulation tissue in group 2 compared to group 1, as evidenced by a larger ($p<0.05$) value of the specific volume of fibrous and vascular components, a smaller ($p<0.05$) value of the specific volume of cellular component.

In the bone cavity on the 7th day compared to the previous period in group 1 and especially in group 2 a more pronounced decrease in blood clot elements and alteratively changed tissues, an increase in the volume of granulation tissue, and the appearance of connective and osteogenic fibroreticular tissues were revealed (Fig. 2). On the 7th day compared to the 3rd day the granulation tissue became more mature, as evidenced by an increase ($p<0.05$) of the specific volumes of fibrous (in group 1 – (35.3±0.81)%, in group 2 – (45.8±0.49)%) and vascular (in group 1 – (20.8±0.44)%, in group 2 – (39.0±0.71)%) components, a decrease ($p<0.05$) of the specific volume of cellular component (in group 1 – (43.9±0.81)%, in group 2 – (15.2±0.8)%).

Also, compared to the previous term, on the 7th day, in some of the fields of vision, the granulation tissue turned into connective tissue. In group 1, hemodynamic disturbances in the granulation and connective tissues similar to the 3rd day were found (Fig. 3). In group 2, compared to group 1, the

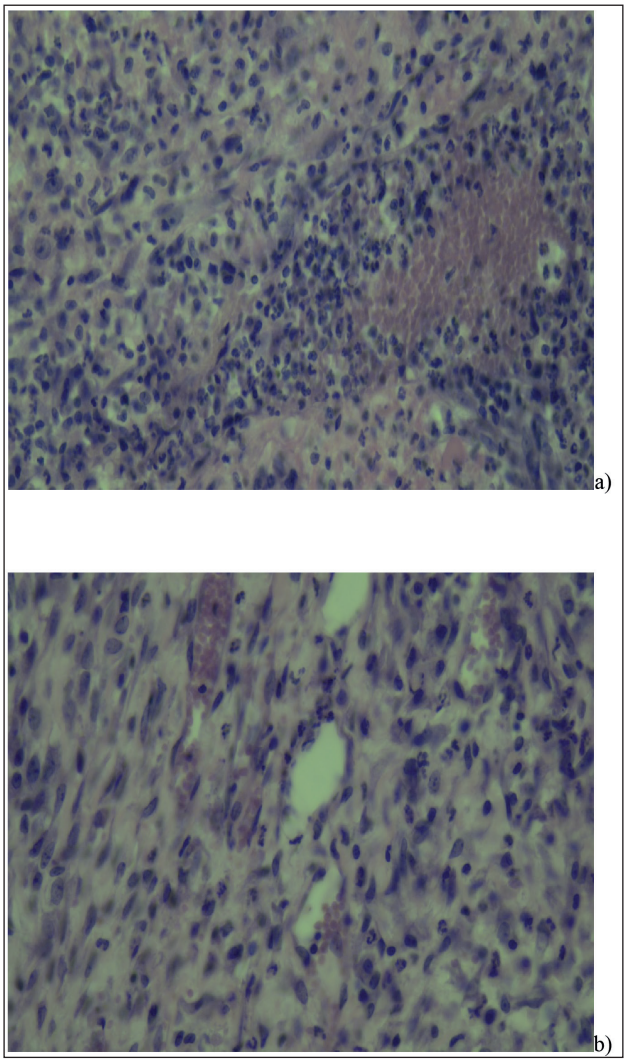

Fig. 1. Immature granulation tissue located in the bone defect cavity of the lower jaw of a rat from group 1 (a) and group 2 (b). Hemodynamic disturbances in granulation tissue in group 1 (a). Hematoxylin and eosin staining, × a) 400, × b) 400.

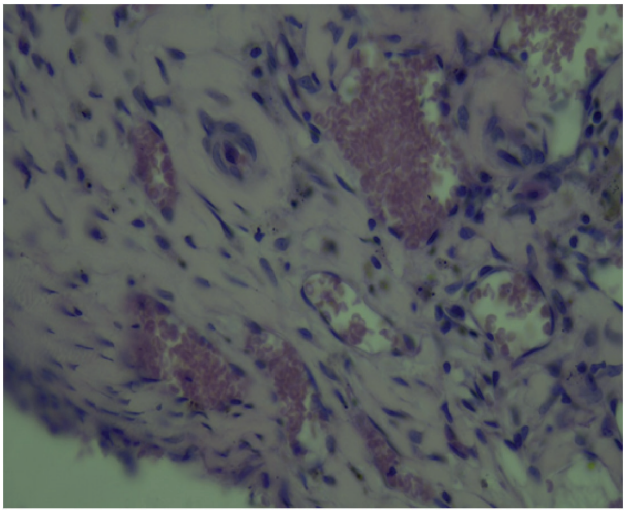

Fig. 3. Hemodynamic disturbances in granulation tissue located in the bone defect cavity of the lower jaw of a rat from group 1. Cells with pronounced osteoblastic activity are mainly around the blood vessels. Hematoxylin and eosin staining, ×400.

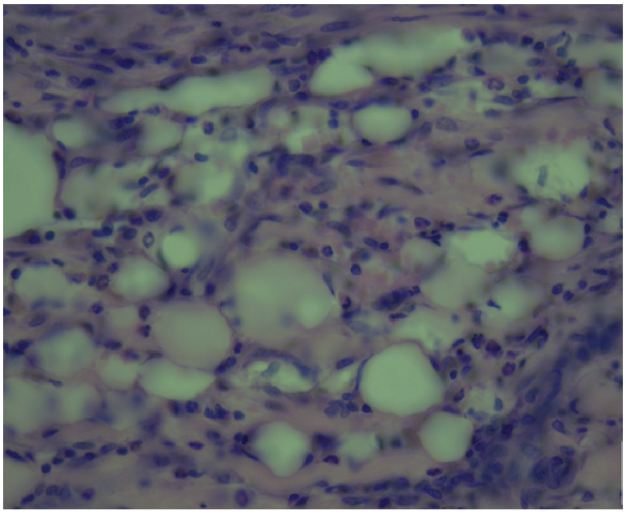

Fig. 4. Groups of adipocytes in the regenerate filling the bone cavity of the lower jaw of a rat from group 2. Hematoxylin and eosin staining, ×400.

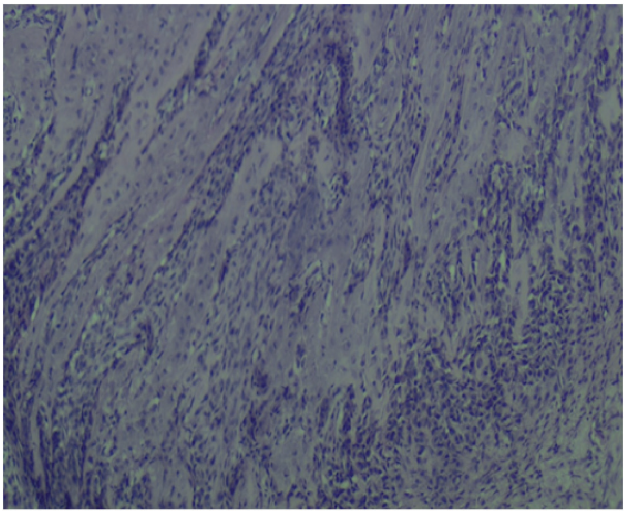

Fig. 2. The bone cavity in the lower jaw of a rat from group 1 is filled with regenerate, represented by granulation, connective and osteogenic fibroreticular tissues. Hematoxylin and eosin staining, ×400.

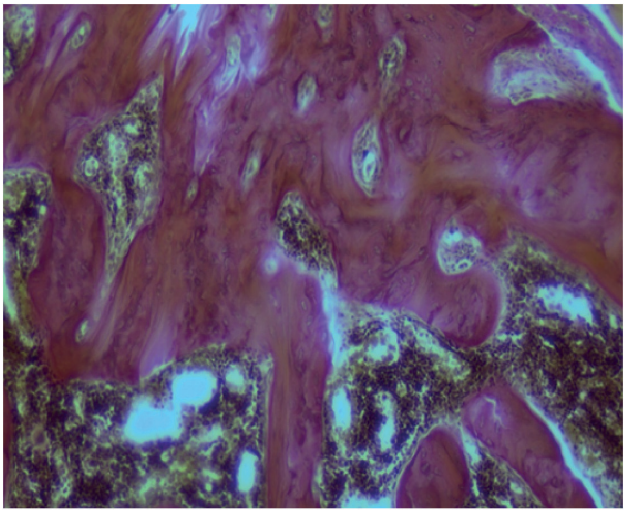

Fig. 5. Lamellar bone tissue from the regenerate area in a rat from group 2. Staining with picrofuchsin according to van Gieson, × 400.

specific volumes of fibrous and vascular components had a significantly ($p<0.05$) greater value, the specific volume of cellular component was significantly ($p<0.05$) smaller, which indicated a greater degree of granulation tissue maturity in group 2.

The appearance of osteogenic fibroreticular tissue in the regenerate in both groups, from our point of view, was due to the activation of the proliferative potential of osteoblastic elements of the bone tissue bordering the cavity; the appearance in granulation and connective tissues of cells with pronounced osteoblastic activity, mainly around the vessels (Fig. 3). The latter microscopic findings were more pronounced in group 2 compared to group 1. In group 2, groups of adipocytes of different sizes and round-oval shapes were found in the bone cavity between the connective tissue fibers, in the areas of granulation tissue (Fig. 4).

On the 14th day, the regenerate filling the bone cavity in the lower jaw of rats of both groups was represented by granulation, connective, osteogenic fibroreticular and lamellar bone tissues. In these animals compared to 7th day in group 1 the volume of granulation, connective and osteogenic fibroreticular tissue increased, but in group 2 the volume of granulation and connective tissue decreased and the volume of osteogenic fibroreticular tissue increased. In group 2 on the 14th day compared to the 7th day the number of adipocytes in the granulation and connective tissues localization increased. On the 14th day in group 2 compared to group 1 the volume of granulation and connective tissues was smaller, while the volume of osteogenic fibroreticular and lamellar bone tissues was larger, which indicated more intensive and qualitative healing processes.

More intensive bone defect healing processes in group 2 compared to group 1 were also evidenced by the results of the morphometric study of granulation tissue. Thus, in group 2 compared to group 1, the specific volumes of fibrous (in group 1 – (64.3±1.00)%, in group 2 – (79.7±0.76)%) and vascular (in group 1 – (5.7±0.45)%, in group 2 – (13.9±0.31)%) components had a significantly ($p<0.05$) greater value, but the specific volume of cellular component (in group 1 – (30.0±0.94)%, in group 2 – (6.4±0.81)%) had a significantly ($p<0.05$) smaller value.

In group 2, in the lamellar bone tissue, the intertrabecular spaces were filled with connective tissue, with the presence of foci of hematopoiesis in some of them. Areas of connective tissue metaplasia into bone tissue were also noted in group 2.

On the 28th day, the bone cavity in both groups was filled with connective, osteogenic fibroreticular and lamellar bone tissues. In group 2, compared to group 1, the healing processes of the bone defect occurred more intensively, which was evidenced by a smaller volume of connective and osteogenic fibroreticular tissues, a larger volume of lamellar bone tissue (Fig. 5). In group 2, compared to the 14th day, adipocyte clusters were visualized in the connective tissue locations, the number of which was significantly smaller. Foci of hematopoiesis were found in the intertrabecular spaces of lamellar bone tissue, the number of which was significantly greater in group 2 compared to group 1. The bone beams in the lamellar bone tissue did not have an orderly spatial orientation in both groups. Consequently, on the 28th day of the experiment in rats of both groups, reparative osteogenesis in the lower jaw continued, but this process occurred more intensively in group 2, as evidenced by the fact that the majority of the regenerate volume was lamellar bone tissue.

DISCUSSION

The bone tissue of the lower jaw is characterized by good regenerative properties, due to which its damage can be restored. Regeneration of bone tissue, as is known, is a staged process that occurs rather slowly [8]. Data from molecular biology, biochemistry, morphology and genetics made it possible to distinguish the following stages of reparative osteogenesis: alterative-resorptive; degenerative-inflammatory and proliferative; synthetic; remodeling and finishing [9, 10].

The search of methods for stimulating reparative osteogenesis is an urgent issue today and a priority for scientific research. Data from the literature and the results of a complex experimental and morphological study conducted by the authors prove the effectiveness of the method of electrical stimulation of reparative osteogenesis in the lower jaw. The latter occurs through direct osteogenesis, but the regeneration process, as is known, can occur through indirect osteogenesis [11]. The positive effect of electrical stimulation revealed by the authors is due to several mechanisms.

The results of the authors' morphometric study of the granulation tissue, which was one of the components of the regenerate that filled the bone defect, revealed significantly higher values of the specific volume of blood vessels during electrical stimulation compared to the control group. This fact indicates that the applied method stimulates angiogenesis. Blood vessels, as is known, transport oxygen, nutrients, soluble factors, numerous cells, etc. [12]. Survey microscopy and morphometry showed that neovascularization stimulated the maturation of granulation tissue and its further transformation into connective tissue, and activated the proliferative potential of fibroblastic cells and cells with osteoblastic activity.

Neovascularization is important in the processes of reparative osteogenesis. Bone tissue renewal can be outlined as a complicated mechanism centered on the interaction between osteogenic and angiogenic events capable of leading to bone formation and tissue renovation [12]. In the conditions of insufficient angiogenesis and hypoxia, the intensity of the reparative osteogenesis processes decreases [13]. Some studies have shown that under hypoxic conditions, the regeneration process occurs through indirect osteogenesis [14].

Electrical stimulation acted as a factor activating macrophage cells, which contributed to a more intensive cleansing of the bone cavity from blood clot fragments and alteratively changed tissues, which also had a positive effect on the processes of reparative osteogenesis.

An interesting fact was the presence of groups of adipocytes

of different sizes and shapes in the loci of connective and granulation tissues in the regenerate, which filled the bone cavity in the lower jaw of rats in cases of electrical stimulation. The presence of these cells suggests their participation in the processes of reparative osteogenesis.

Some studies have shown that adipocytes play an important role in the reparative osteogenesis of maxillofacial defects. The effectiveness of the use of mesenchymal stem cells obtained from adipose tissue in the treatment of bone tissue defects has been proven. These cells are characterized by an active ability to directly differentiate into mature osteoblasts; produce chemokines which useful for facilitating the homing of endogenous stem cells to the site of the bone defect [15]. In the study conducted by the authors, under the conditions of electrical stimulation, adipose tissue was transformed into bone tissue in the regenerate that filled the bone cavity.

The use of electrical stimulation for reparative osteogenesis activation has been studied for many years in both in vitro and in vivo models using numerous approaches ranging from different configurations, electrode parameters, and electrical current sources [16-18]. Numerous clinical and experimental studies have proven the effectiveness of electrical stimulation due to the effect on the migration, proliferation, differentiation, adhesion, and function of bone-forming cells; activation the transformation of stem cells into osteogenic cells [18-20]; involvement in the locus of bone tissue damage the cells necessary for healing (neutrophils, macrophages, fibroblastic cells, etc.); activation chondrogenesis in cases of regeneration through indirect osteogenesis [18]; activation nervous regulation, thereby activating microcirculation.

The effect of electrical stimulation on cell apoptosis remains unclear and controversial. Some studies report stimulation of cell apoptosis, while other studies describe a reduced effect or its absence [18].

Previous studies conducted by the authors showed a positive effect of combined use of hydroxyapatite-containing osteotropic material ("Biomin GT") and electrical stimulation in the treatment of bone tissue defects of the lower jaw in rats [21].

CONCLUSIONS

A comprehensive clinical and experimental study conducted by the authors proved that electrical stimulation activates the reparative osteogenesis in the lower jaw, which occurs through direct osteogenesis and does not finish on the 28th day of the experiment.

The positive effect of electrical stimulation is due to a decrease in the severity of hemodynamic disorders, activation of angiogenesis in granulation tissue, which is one of the components of the regenerate that fills the bone defect, matures and turns into connective tissue; stimulation of the proliferative potential of fibroblastic cells and cells with osteoblastic activity in granulation tissue; increasing the proliferative potential of osteoblastic elements of bone tissue bordering the cavity; stimulation of macrophage cells and processes of cleansing the bone cavity from fragments of a blood clot and alteratively changed tissues; formation of clusters of adipocytes in the loci of connective and granulation tissue of the regenerate; the process of metaplasia of connective tissue into bone tissue; an increase of the foci of hematopoiesis in the intertrabecular spaces of lamellar bone tissue.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.