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HISTOLOGICAL CHANGES OF BONE TISSUE IN THE PERFORATION DEFECT SITE OF THE RAT MANDIBLE WHEN USING HEPATOPROTECTOR IN ODSTRUCTIVE HEPATITIS

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The purpose of the study was to experimentally investigate the features of reparative regeneration of the mandibular defect in rats with obstructive hepatitis against the background of hepatoprotector administration. An experimental study was performed on 60 white male Wistar rats, weighing 240-270 g. In the process of work, the rats were divided into 3 groups (20 rats in each one): control - included healthy rats with mandibular trauma; experimental group 1 - rats with jaw injury and simulated obstructive hepatitis; experimental group 2 - rats with mandibular injury + obstructive hepatitis + complex hepatoprotector. The experiment revealed that obstructive hepatitis impairs bone tissue healing in the site after the traumatic defect. The use of hepatoprotector, in experimental obstructive hepatitis, is a very effective measure for the processes of bone regeneration at the site of perforation.

Key words: experiment, rats, mandibular injury, obstructive hepatitis, hepatoprotector

The work is a fragment of the research project "Development of methods for surgical treatment of patients with pathology of the maxillofacial area, taking into account the correction of comorbidities", state registration No. 0118U005403.

The steady increase in the number of facial skeleton fractures and injuries of the maxillofacial area remains one of the important problems of today [2, 3, 4]. The problems of maxillofacial traumatology also include solution of the frequent complications' etiopathogenesis. Among facial injuries, the leading place is occupied by fractures of the upper and lower jaw in the structure of general traumatism. Fractures of the facial skeleton bones, among the injuries of the maxillofacial area, occur in 75-87% of cases [2, 3, 4, 6]. Among all examined and hospitalized patients, injuries of the maxillofacial area make about 15-38% [2, 3].

The increase in the total number of injuries also leads to an increase in the frequency of maxillofacial injuries and their complications. This is particularly true in patients with concomitant pathology [6], which can have a significant impact on the course of inflammatory processes. It should also be noted that an important factor in the development of inflammatory complications is the microbial factor. In the area of soft tissue wounds or fractures of the jaws there is a sequence of pathological local and general changes, which subsequently leads to complications (suppuration of bone wound, post-traumatic osteomyelitis, pseudarthrosis, abnormal mobility of bone fragments, secondary bleeding, post-traumatic sinusitis or neuritis, disturbed bite) [2, 3, 6].

Taking into account the above factors, the problem of complications should be considered and explained in the perspective of its association with the presence of comorbidities, including diseases of the liver and hepatobiliary system. This is primarily due to the high prevalence of liver disease, which occurs in almost 70% of the population [1, 5].

When the integrity of the maxillofacial area tissues is repaired, reparative regeneration of bone and soft tissue wound occurs due to the property of a living macroorganism to tissue repair, by forming a connective tissue matrix, followed by ossification of the fracture site with restoration of previous tissue structure [2, 3, 6]. An important task of dentists and maxillofacial surgeons in clinical settings, to improve the conditions of jaws fractures regeneration and recovery in inflammatory processes is to prevent the development of complications that may occur.

We have not found information about experimental studies of the maxillofacial tissues regeneration against the background of the hepatobiliary system pathology, and it needs further study and explanation.

The purpose of the work was to experimentally study the features of reparative regeneration of the mandible defect in rats with obstructive hepatitis against the background of hepatoprotector administration.

Materials and methods. We have performed an experimental study on 60 white male Wistar rats. Rats were on a common diet, had free access to water and food and standard living conditions in the cages of the vivarium at M.I. Pirogov VNMU. Age of animals was 5-6 months. The weight of rats ranged from 240 to 270 g.

A large number of mandibular fracture models in laboratory animals is known, but not all of these techniques permit to obtain objectification and standardization of the fracture, which in its turn will not permit to give an objective assessment [2, 3, 6]. In the experiment, we used the technique of causing a defect in the area of mandibular angle in rats with a surgical drill with a diameter of 1 mm, with the rotation rate of up to 10,000 revolutions per minute. This permitted to obtain a standard post-traumatic defect of the mandible and to objectively observe the regeneration processes [2, 6].

In the study process, the rats were divided into 3 groups:

1. Control - 20 rats - study of histological changes in the bone tissue of the mandible in healthy rats with trauma of the mandible at the site of the defect.

2. Experimental group 1 - 20 rats - study of histological changes in the bone tissue of the mandible in rats with trauma of the mandible at the site of the defect in obstructive hepatitis, obtained by ligation and transection of the common bile duct.

3. Experimental group 2 - 20 rats - study of histological changes in the bone tissue of the mandible in rats with trauma of the mandible at the site of the defect in obstructive hepatitis, obtained by ligation and transection of the common bile duct, which on the day of the jaw injury and the following two weeks, were added complex "Quertulin" hepatoprotector to the food at the dose of 200 mg per kilogram of rat weight.

"Quertulin" is a complex hepatoprotective drug containing quercetin bioflavonoid, inulin prebiotic, calcium citrate (permission of the Ministry of Health of Ukraine № 05.03.02. - 06/44464 dated 17.05.2012).

Inulin has an antidisbiotic effect, stimulating the growth of probiotic microflora and eliminating the dysbiosis phenomena.

Quercetin has P-vitamin activity, antioxidative, membrane-protective and hepatoprotective action.

Calcium citrate is the most easily digestible form of calcium, which stimulates bone tissue mineralization, eliminating the osteoporosis phenomena.

In the course of the experimental study, we traced the features of post-traumatic mandibular bone defects regeneration. Quantitative assessment of histological changes was performed using the analysis of morphometric parameters: specific volume (in %) of fibroreticular tissue in the center of bone regeneration, specific volume (%) of blood vessels, specific volume (in %) of bone trabeculae in the center of bone regeneration, the number of osteoblasts in a certain area in the center of bone regeneration, specific volume (%) of bone marrow in the center of bone regeneration. The study was performed on the 7th, 14th, 30th, 60th days of the study.

The study was carried out in compliance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine №3447-IV "On protection of animals from cruel treatment", general ethical principles of animal experiments, approved by the First National Congress of Ukraine on Bioethics (2001).

Numerical values are statistically processed with calculation of mean values (M) and standard error (±m). The probability of discrepancies in the mean values (p) was determined using the Student's t test. Discrepancies were considered reliable at $p < 0.05$.

Results of the study and their discussion. As a result of the experiment, in rats of the control group (n = 20), the features of bone damage regeneration in the area of the induced defect were observed. From the data in table 1, it is seen that the specific volume of fibroreticular tissue in the center of bone regeneration on the 7th day is predominant over other elements and makes about 91.4%.

Table 1

Morphometric parameters of regenerative tissues at the site of injury of the mandibular angle in the dynamics of the experiment in rats of the control group (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	91.4±0.94	56.3±0.71	48.2±0.51	12.4±0.22
specific volume (%) of blood vessels	3.2±0.05	2.0±0.05	1.6±0.05	0.5±0.01
specific volume (%) of bone trabeculae	1.8±0.04	12.9±0.84	48.0±0.19	72.2±0.68
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2	3.5±0.04	5.7±0.15	2.0±0.06	1.0±0.05
specific volume (%) of bone marrow	0	0	1.6±0.04	3.8±0.05

The presence of individual bone trabeculae in this period of the study is explained primarily not by their new creation, but by the remnants of former bone trabeculae that were at the site of perforation and damage before this injury. In addition, it is worth noting the increased number of osteoblasts per area unit of bone trabeculae. Such an increased concentration of them in the bone trabeculae indicates that the old bone trabeculae are also involved into the processes of bone regeneration at the defect site. The specific

volume of blood vessels on the 7th day of the experiment in the center of bone regeneration reaches 3.5%, and these blood vessels are located almost exclusively in the area of fibroreticular tissue.

We also found that on the 7th day there are no formed elements of bone marrow observed, although in fibroreticular tissue there is a significant presence of cells, which morphologically can be called lymphoid cells, which are round-shaped with a round nucleus and a narrow rim of the cytoplasm. It is known that cells with the above morphology can be either lymphocytes or stem (polypotent) cells, which in the future the elements of the bone marrow are formed of.

According to the data obtained, as can be seen from table 1, the specific volume of fibroreticular tissue in the center of bone regeneration in the dynamics of the experiment without external influence in animals of the control group decreases and on the 60th day is 12.4±0.22% against 91.4±0.94% on the 7th day. Along with this, in the dynamics of the experiment in the center of bone regeneration also decreases the specific volume of blood vessels, although on the 60th day these blood vessels are already localized not only in fibroreticular tissue, but also in the bone marrow, which is also already available on the 30th and moreover on the 60th day.

The specific volume of bone trabeculae up to the 14th day grows more than by 5 times compared to the seventh day, up to the 30th day it still grows and on the 60th day of the experiment the specific volume of bone trabeculae reaches more than 72 %, i. e. bone trabeculae in this period already constitute most of the elements in the bone regeneration zone (fig. 1).

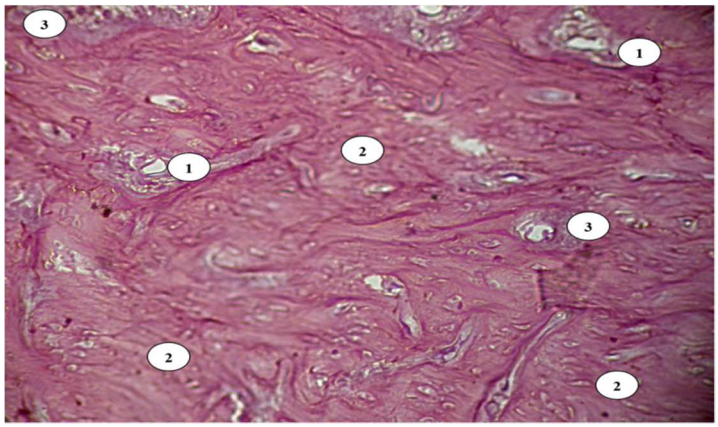

Fig. 1. Bone wound of the rat lower jaw at the site of its perforation on the 60th day of the experiment in the control group (n = 20). 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin. Ob.10^x. Oc. 20^x.

The mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm2 decreases at a relatively slow rate. It should be noted that on the 14th day compared to the 7th, there is no reliable decrease in the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit ($p > 0.05$), except that there is only a tendency to decrease, but on the 30th day compared to the 7th day, the changes, although not pronounced, are still statistically significant ($p < 0.05$). The same can be noted on the 60th day of the experiment in rats of the control group, when the mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area has the lowest value among all periods of the experiment.

As mentioned above, the obvious elements of the bone marrow are only present in the histological materials of the damage area in the mandible of rats on the 30th and 60th day of the experiment. The bone marrow was dominated by hematopoietic elements at different stages of development with a predominance of lymphoid cells, single thin-walled slit-like blood vessels and individual lymphocytes. Thus, a certain sequence of histological changes and a sufficiently high activity of regenerative elements involved in the construction of new bone tissue and restoration of the bone defect were revealed.

Studies of histological changes in the bone tissue of the rat mandible at the site of its injury in obstructive hepatitis, showed that the specific volume of fibroreticular tissue in the bone regeneration center on the 7th day is dominant over other elements and is more than 90% (table 2).

Table 2

Morphometric parameters of mandibular tissues at the site of injury in obstructive hepatitis, without treatment in rats of experimental group 1 (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.1±0.88	84.5±0.73	74.6±0.58	32.8±0.24
specific volume (%) of blood vessels	3.7±0.08	3.4±0.09	3.2±0.05	1.7±0.02
specific volume (%) of bone trabeculae	1.4±0.05	5.6±0.14	14.8±0.16	53.4±0.64
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2	3.8±0.08	3.5±0.10	3.3±0.06	2.8±0.04
specific volume (%) of bone marrow	0	0	0	2.3±0.06

Experimental data showed that the specific volume of fibroreticular tissue in the center of bone regeneration in rats of the experimental group 1 is almost no different from the control group on the seventh day.

Individual bone trabeculae in this period of the study are explained, of course, not by their new creation, but by the remnants of former bone trabeculae, which were at the site of perforation before the injury. The increased number of osteoblasts per area unit of bone trabeculae should also be noted. Such an increased concentration of them in the bone trabeculae indicates that the old bone trabeculae are also involved in the processes of bone regeneration in the defect site.

The specific volume of blood vessels on the 7th day of the experiment in the center of bone regeneration does not reach even four percent, and these blood vessels are located almost exclusively in the area of fibroreticular tissue. It should also be noted that on the 7th day there are no formed elements of the bone marrow, although in fibroreticular tissue there is a significant presence of cells, which morphologically should be called lymphoid cells. These lymphoid cells are round in shape with a round nucleus and a narrow rim of the cytoplasm. It is known that cells with the above morphology can be either lymphocytes or stem (polypotent) cells, which in the future the elements of the bone marrow are formed of.

As it can be seen from table 2, the specific volume of fibroreticular tissue in the bone regeneration center in the dynamics of the experiment with ligation of the common bile duct decreases and on the 60th day it is reduced by about three times compared to the 7th day.

In the dynamics of the experiment in the center of bone regeneration during ligation of the common bile duct, we found that the specific volume of blood vessels decreases, although on the 60th day these blood vessels are localized not only in fibroreticular tissue but also in bone marrow, which is also already available on the 60th day, although on the 30th day of the experiment the formed elements of the bone marrow in the center of bone regeneration can not be found, as in the previous periods of the experiment.

The specific volume of bone trabeculae up to the 14th day in rats of experimental group 1, grows more than by 4 times compared to the seventh day, and up to the 30th day it grows even more and on the 60th day of the experiment the specific volume of bone trabeculae is more than 50%, i. e. bone trabeculae in this period already make the most part of elements in the bone regeneration zone.

The mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2 decreases at a relatively slow rate. It should be noted that on the 14th day compared to the 7th day there is not a probable decrease in the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit ($p > 0.05$), except that there is only a downward trend, but on the 30th day compared to the 7th day, the changes, although not expressed morphologically, but still in the quantitative composition of cells are statistically significant ($p < 0.05$). Similar indices can be noted on the 60th day of the experiment, when the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit has the lowest value among all periods of the experiment (fig. 2).

As mentioned above, the obvious elements of the bone marrow during ligation of the common bile duct are only present in the histological materials of rats on the 60th day of the experiment. The bone marrow was dominated by hematopoietic elements at different stages of development with a predominance of lymphoid cells, single thin-walled slit-like blood vessels and individual lymphocytes.

Morphometric parameters in the study of jaws bone tissue in the animals of experimental group 2, show a positive effect of “Quertulin” on bone regeneration in the site of its defect (table 3).

Table 3

Morphometric parameters of the mandible hard tissues in the site of injury during ligation of the common bile duct in the dynamics of the experiment under correction with hepatoprotector, in rats of experimental group 2 (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.2±0.83	77.0±0.72	64.3±0.50	21.3±0.25
specific volume (%) of blood vessels	3.7±0.05	3.1±0.05	3.0±0.04	1.1±0.01
specific volume (%) of bone trabeculae	1.5±0.06	7.4±0.6	28.9±0.12	62.5±0.65
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2	3.7±0.09	4.6±0.13	2.7±0.04	1.2±0.03
specific volume (%) of bone marrow	0	0	0	2.8±0.05

The use of “Quertulin” significantly increases the proportion of bone marrow trabeculae on the 60th day compared to similar indices in experimental group 2 (fig. 3).

Morphometric data, presented in table 3, prove that the use of “Quertulin” as a means of correcting bone regeneration in the site of its perforation during ligation of the common bile duct, leads to accelerated regeneration rates from the 7th day of the experiment, as it is indicated by changes in the specific volume of fibroreticular tissue, blood vessels, bone trabeculae and bone marrow ($p < 0.05$) [6].

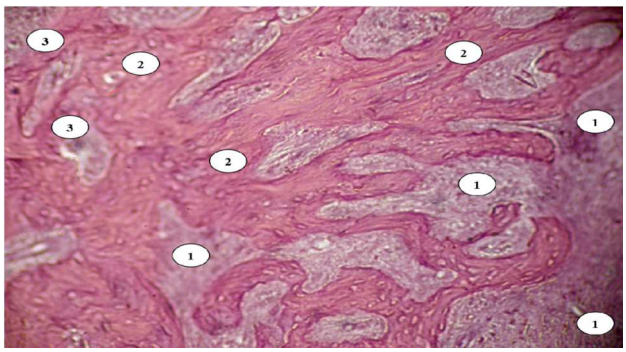

Fig. 2. Bone wound of the rat lower jaw in the site of its perforation during ligation of the common bile duct on the 60th day of the experiment in experimental group 1. 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin.Ob.10^x. Oc. 20^x.

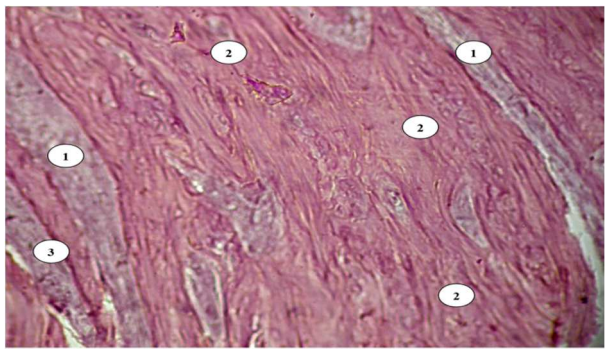

Fig. 3. Bone wound of the rat lower jaw in the site of its injury in obstructive hepatitis on the 60th day of the experiment under the correction with “Quertulin” in experimental group 2. 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin.Ob.10^x. Oc.20^x.

The main patterns of changes in the dynamics of the experiment during ligation of the common bile duct were also preserved concerning the number of osteoblasts and bone trabeculae on the 30th day ($p < 0.05$). Concomitant liver pathology has a negative impact on regenerative processes in bone tissue [2, 3, 5]. Given the multifunctionality of the liver [1, 5], it is the control of its functions that becomes important in patients with traumatic injuries of the facial bones.

When using hepatoprotectors in the complex treatment of patients with fractures of the facial skeleton, one can reduce the number of complications and accelerate the fracture healing.

Conclusion

Експериментальне дослідження показало, що обтураційний гепатит погіршує загоєння кісткової тканини у ділянці після травматичного дефекту. Застосування комплексного гепатопротектора при експериментальному обтураційному гепатиті є досить ефективним заходом для процесів регенерації кістки в місці перфорації. У пацієнтів з переломом нижньої щелепи, при виявленні патології гепатобілірної системи, доцільно використовувати «Квертулін».

Experimental studies have shown that obstructive hepatitis impairs bone healing in the area after a traumatic defect. The use of a complex hepatoprotector in experimental obstructive hepatitis is a very effective measure for the processes of bone regeneration in the site of perforation. In patients with a fracture of the mandible, when pathology of the hepatobiliary system is detected, it is advisable to use “Quertulin”.

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Реферати

ГІСТОЛОГІЧНІ ЗМІНИ КІСТКОВОЇ ТКАНИНИ У ДІЛЯНЦІ ПЕРФОРАЦІЙНОГО ДЕФЕКТУ НИЖНЬОЇ ЩЕЛЕПИ ЩУРІВ ПРИ ВИКОРИСТАННІ ГЕПАТОПРОТЕКТОРА НА ТЛІ ОБТУРАЦІЙНОГО ГЕПАТИТУ

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Метою дослідження було експериментальне вивчення особливостей репаративної регенерації дефекту нижньої щелепи щурів при обтураційному гепатиті на тлі прийому гепатопротектора. Було проведено експериментальне дослідження на 60 білих щурах-самцях масою 240-270 г. У процесі роботи щури були розділені на 3 групи (по 20 щурів у кожній групі): контрольна - включала здорових щурів з травмою нижньої щелепи; дослідницька №1 - щури з травмою щелепи і

ГИСТОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ КОСТНОЙ ТКАНИ В ОБЛАСТИ ПЕРФОРАЦИОННОГО ДЕФЕКТА НИЖНЕЙ ЧЕЛЮСТИ КРЫС ПРИ ИСПОЛЬЗОВАНИИ ГЕПАТОПРОТЕКТОРА НА ФОНЕ ОБТУРАЦИОННОГО ГЕПАТИТА

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Целью исследования было экспериментальное изучение особенностей репаративной регенерации дефекта нижней челюсти крыс при обтурационном гепатите на фоне приема гепатопротектора. Было проведено экспериментальное исследование на 60 белых крысах-самцах линии Вистар массой 240-270 г. В процессе работы крысы были разделены на 3 группы (по 20 крыс в каждой группе): контрольная - включала здоровых крыс с травмой нижней челюсти; экспериментальная №1 - крысы с травмой

модельованим обтураційнім гепатитом; дослідницька №2 - щури з травмою нижньої щелепи + обтураційний гепатит + комплексний гепатопротектор. В результаті експерименту виявили, що обтураційний гепатит погіршує загоєння кісткової тканини в області післятравматичного дефекту. Застосування гепатопротектора, при експериментальному обтураційному гепатиті, досить ефективно для процесів регенерації кістки в місці перфорації.

Ключові слова: експеримент, щури, травма нижньої щелепи, обтураційний гепатит, гепатопротектор.
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челюсти и моделируемым обтурационным гепатитом; экспериментальная №2 - крысы с травмой нижней челюсти + обтурационный гепатит + комплексный гепатопротектор. В результате эксперимента обнаружили, что обтурационный гепатит ухудшает заживление костной ткани в области посттравматического дефекта. Применение гепатопротектора, при экспериментальном обтурационном гепатите, достаточно эффективно для процессов регенерации кости в месте перфорации.

Ключевые слова: эксперимент, крысы, травма нижней челюсти, обтурационный гепатит, гепатопротектор.
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DYNAMICS OF MORPHOMETRIC BONE CHANGES IN THE SITE OF MANDIBULAR PERFORATION DEFECT IN RATS WITH TOXIC HEPATITIS AND USE OF HEPATOPROTECTOR

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The purpose of the work was to experimentally study morphometric changes in the healing of perforation defect of the mandible in rats against the background of toxic hepatitis and the use of complex hepatoprotector. An experimental study was performed on 60 white male Wistar rats weighing 240-270 g. In the experiment process, the rats were divided into 3 groups (20 rats in each group): control - included healthy rats with mandibular trauma; experimental group 1 - rats with jaw injury and simulated toxic hepatitis; experimental group 2 - rats with trauma of the mandible + toxic hepatitis + complex hepatoprotector. The study of histological changes in the bone tissue of the mandible in the site of injury, in toxic hepatitis, justified the positive effect of hepatoprotector on changes in morphometric parameters. The experiment results revealed that toxic hepatitis worsened the morphometric parameters of the mandible perforation defect healing. It is particularly important that the complex hepatoprotector in toxic hepatitis increases the specific volume of bone trabeculae on the 30th and the 60th day and bone marrow on the 60th day, which indicates its positive effect on bone regeneration in the site of perforation.

Key words: experiment, rats, mandibular trauma, simulated toxic hepatitis, complex hepatoprotector.

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Despite the scientific and technological progress and development of mankind in recent years, the number of injuries of the maxillofacial area and their complications still continues to grow [2, 3, 4, 5, 7, 8]. An important place is given to the solution and study of the possible etiopathogenesis of post-traumatic complications. Among the traumatic injuries of the face, the most common are fractures of the lower jaw, nasal bones, zygomaticoorbital complex, upper jaw. Injuries of the maxillofacial area make 15-38% among all examined and hospitalized in the clinic [2, 3, 5, 10, 11]. Maxillofacial fractures among all injuries of the facial skeleton occur in 75-87% of cases according to various authors [2, 3, 5, 6, 8, 11]. In addition, it is known that the share of maxillofacial injuries grows by 3-4% annually, both in our country and abroad. At the same time, about 80% of mandibular fractures occur in men of the most employable age - 20-40 years. This fact explains the urgency of the problem of treating fractures of the facial skeleton and their complications. Fractures of the facial skeleton bones are most frequently of transport and home accident origin [2, 5, 7].

The increase in the total number of injuries also leads to an increase in the frequency of maxillofacial injuries and their complications. All post-traumatic complications of non-gunshot mandible fractures can be divided into early (bone wound suppuration, secondary displacement of fragments, lymphadenitis, abscess, phlegmon, thrombophlebitis of facial veins) and late ones (post-traumatic osteomyelitis, sinusitis, delayed consolidation of fragments, pathological mobility of fragments, malunion, false joint, post-traumatic deformity). Of particular importance is the problem of post-traumatic complications in patients with comorbidities [1, 2, 3, 4, 6, 9], which can have a significant impact on the occurrence and course of post-traumatic inflammatory processes. It should also be remembered that the immediate cause of purulent-inflammatory complications is infection of the area affected by the microflora of the oral cavity and periapical foci of chronic infection. In the injury area there is a sequence of