UDC 616.716.4-001.5-089 https://doi.org/10.26641/2307-0404.2021.3.242154

# THERAPY OF DELAYED CONSOLIDATION OF MANDIBLE FRACTURES

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***Цитування: Медичні перспективи. 2021. Т. 26, № 3. С. 139-145***
***Cited: Medicni perspektivi. 2021;26(3):139-145***

**Key words:** *fracture of the mandible, delayed consolidation, osteogenesis, fibrin-enriched platelets, bone morphogenetic protein*
**Ключові слова:** *перелом нижньої щелепи, сповільнена консолідація, остеогенез, збагачений тромбоцитами фібрин, морфогенетичний білок кістки*
**Ключевые слова:** *перелом нижней челюсти, замедленная консолидация, остеогенез, обогащенный тромбоцитами фибрин, морфогенетический белок кости*

**Abstract. Therapy of delayed consolidation of mandible fractures. Idashkina N.H., Gudarian O.O., Samoilenko I.A., Shandyba S.I.** *The aim of the study is to improve the effectiveness of treatment for delayed consolidation of mandibular fractures by developing and clinical testing of integrated therapy using growth factors and bone morphogenetic protein-2. Clinical material is based on the study of 62 patients with the problem of mandibular fractures consolidation. The examinations of bone density were carried out on a cone-beamed computerized tomograph Planmeca Promax 3D (Finland) with an X-ray emitter of 85 kV 5-7 mA on the day 7 and 21 of the study. The evaluation of the density of jaw bone tissue was conducted by U. Lekholm and G. Zarb (1985) classifications, and by S. Mish (1990). Bone density of more than 850 units was considered as an intact dense bone, the values from 350 to 850 units - as a relatively intact, loose bone, and less than 350 Hounsfield units - local osteoporosis. Statistical processing of materials was carried out using standard methods of variation statistics using the STATISTIKA (ver. 6.1; Statsoft Inc., USA, No. AGAR 909E415822FA). Use in the therapy of delayed consolidation of mandible fractures of the developed complex, which includes strontium ranelate – a drug with osteotropic action, antioxidant Mexidol, immunomodulator of recombinant human interleukin-2, and a local introduction of fibrin-enriched platelets containing numerous growth factors along the fissure of mandible fracture, or recombinant bone morphogenetic protein-2 in more complicated cases. The improvement of reparative processes was in 58 patients. In any case there was no need to carry out additional surgical interventions for osteosynthesis or bone «grafting». The basic program on care of patients with a delayed consolidation of mandible fractures should affect all pathogenesis components of this complication: it should include osteotropic drugs, antioxidants and immunomodulators. Involvement of platelet-rich fibrin in the integrated therapy positively affects the quality of bone regenerate and treatment terms, ensuring the normalization of clinical and laboratory parameters up to the day 21. The best optimization of reparative osteogenesis in the complex therapy of delayed consolidation is facilitated by the additional injection of recombinant human bone morphogenetic protein-2. This tactic allowed to ensure its favorable course by the type of initially delayed adhesion in all patients (8 out of 8).*

**Реферат. Терапія сповільненої консолідації переломів нижньої щелепи. Ідашкіна Н.Г., Гудар'ян О.О., Самойленко І.А., Шандиба С.І.** *Мета дослідження – підвищення ефективності лікування сповільненої консолідації переломів нижньої щелепи шляхом розробки та клінічного тестування інтегрованої терапії з використанням факторів росту та морфогенетичного білка кістки-2. Клінічний матеріал ґрунтується на дослідженні 62 пацієнтів з проблемною консолідацією переломів нижньої щелепи. Для визначення мінеральної щільності кістки обстеження проводили на конуснопроменевому комп'ютерному томографі Planmeca Promax 3D (Фінляндія) з рентгенівським випромінювачем 85 кВ 5-7 мА на 7-у та 21-у добу дослідження. Оцінка щільності кісткової тканини щелеп проводилась за класифікаціями U. Lekholm і G. Zarb (1985), а також за C. Mish (1990). Кісткова тканина зі щільністю більше 850 одиниць розглядалася як інтактна щільна кістка, з показниками від 350 до 850 одиниць – як відносно інтактна, пухка кістка, менше 350 одиниць Хаунсфілда – локальний остеопороз. Статистичну обробку матеріалів здійснювали стандартними методами варіаційної статистики із використанням пакета прикладних програм STATISTIKA (версія 6.1; Statsoft Inc., USA) (ліц. № AGAR 909E415822FA). У терапії сповільненої консолідації переломів нижньої щелепи було застосовано розроблений комплекс, що включає стронцію ранелат – препарат з остеотропною дією, антиоксидант*

*Мексидол, рекомбінантний імуномодулятор інтерлейкін людини-2 та місцеве введення збагаченого тромбоцитами фібрину, що містить численні фактори росту вздовж лінії перелому нижньої щелепи або морфогенетичного білка кістки-2 у більш складних випадках. Спостерігалось покращення репаративних процесів у 58 хворих. У будь-якому випадку не було необхідності проводити додаткові хірургічні втручання для остеосинтезу або графтингу кістки. Основна програма лікування хворих із затримкою консолідації переломів нижньої щелепи повинна впливати на всі компоненти патогенезу цього ускладнення: вона має включати остеотропні препарати, антиоксиданти та імуномодулятори. Включення до комплексної терапії збагаченого тромбоцитами фібрину позитивно впливає на якість кісткового регенерату та строки лікування, забезпечуючи нормалізацію клініко-лабораторних показників у строки до 21-ї доби. Найкраще оптимізації репаративного остеогенезу в комплексній терапії сповільненої консолідації переломів нижньої щелепи сприяє додаткове ін'єкційне введення рекомбінантного морфогенетичного білка кістки-2. Така тактика дозволяла забезпечити сприятливий перебіг за типом первинно відтермінованого зрощення у всіх пацієнтів (8 з 8).*

The work is a fragment of the research project of the Oral Surgery, Implantology and Periodontology Department of SE «Dnipropetrovsk Medical Academy of Health Ministry of Ukraine»: «Development of methods for the prevention of complications in the treatment of inflammatory state and traumatic injuries in the maxillofacial area», state registration No. 0113U005253 and applied research carried out in 2020-23 at the expense of the government funding "The prognosis, prevention and treatment of delayed consolidation of bone tissue in patients with fractures of the jaws" (according to the Order of the Ministry of Health of Ukraine from November 17, 2020 No. 2651).

According to official statistics, the absence of consolidation of the mandible fractures (MF) in 50 days from the onset of treatment is observed in 2.4-14% of cases, while the actual situation is actually worse [9, 11].

In modern literature, which deals with the recommendations for the treatment of delayed consolidation, attention is focused on two approaches of solving the problem: stable mechanical fixation and effect on biological osteogenesis [2]. Recently in most of these works issues concerning either the development of techniques of bone grafting, or the search for the best materials for it that would meet certain requirements are considered: the materials would be biocompatible and non-allergenic, possess osteoinductive qualities or at least being sufficiently porous, should hold the blood clot, and their surface should be electrically active, able to involve osteogenic cells and reject microorganisms, preventing the development of pathogenic bacteria. It is desirable that the surface could perform the role of conductor of bone growth inducers, antibiotics, corticosteroids and others [3].

An alternative therapeutic approach is the use of osteoconductive extracellular matrix, osteoinductive proteins and often osteogenic cells as bone grafting. Bone morphogenetic proteins (BMP) BMP-2 and BMP-7 have already been approved by the FDA (Food and Drug Administration, USA) but they still require clarification of the dosage and application features [7, 10, 14].

At the heart of osteoinductive and stimulated osteogenesis is the activation by morphogenetic proteins of the committed cells – precursors of osteoblasts in the periosteum and endosteum or polypotent stem cells of the connective tissue in the bone marrow [4].

Currently 15 types of BMP that are active at different stages of phenotyping of precursor cells in osteoblasts have been isolated and identified from bone tissue [13].

According to modern ideas, the BMP complex has an impact on differentiation of polypotent stem cells into osteoblasts, on bone cells, accelerating maturation and calcification of bone matrix. The morphogenetic proteins BMP-2, BMP-3, BMP-4, BMP-6 and BMP-7 determine the pathway for differentiation of polypotent mesenchymal cell lines into the osteoblastic line [12].

Along with BMP bone tissue contains growth factors – TGF-p, PDGF, IGF-I, IGF-II, bFGF, aFGF. They are integrated with cytoplasmic receptors of target cells, activate intracellular enzymes, their multi-stage (cascade) system.

The local application of various growth factors affects the proliferation and differentiation of precursors of osteogenic cells in their cultures with the formation of bone tissue, including several congenital and acquired craniofacial defects [6, 8].

Thus, growth factors and bone morphogenetic proteins can stimulate the synthesis of bone collagen proteins by osteoblasts and replenish the latter by the effect on the differentiation of their precursors [1].

Currently, BMP and growth factors are available and used in clinical practice in some countries, however, have not yet been widely used in Ukraine [5].

The aim of the study is to improve the effectiveness of delayed consolidation of MF treatment by developing and clinical testing of integrated therapy using growth factors and bone morphogenetic protein BMP-2.

**MATERIALS AND METHODS OF RESEARCH**

Clinical material is based on the study of 62 patients with the problem of MF consolidation collected over the period from 2010 to 2016 at the clinic of SE "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", being referred from community-based clinical facilities after the termination of MF, that is 1 month after the reposition and fixation of fragments, carried out under inpatient conditions, but which retained the mobility of the fragments in the fracture zone.

Thus, the diagnosis of delay osseous consolidation of MF in these conditions was the resultant and made at the end of the immobilization period.

Treatment of 48 patients was performed by the method of double-jawed splinting, in 14 patients the method of osteosynthesis with titanium miniplates was used. The sample included patients with satisfactory quality of the primary reposition only (confirmed on X-ray images immediately after splinting).

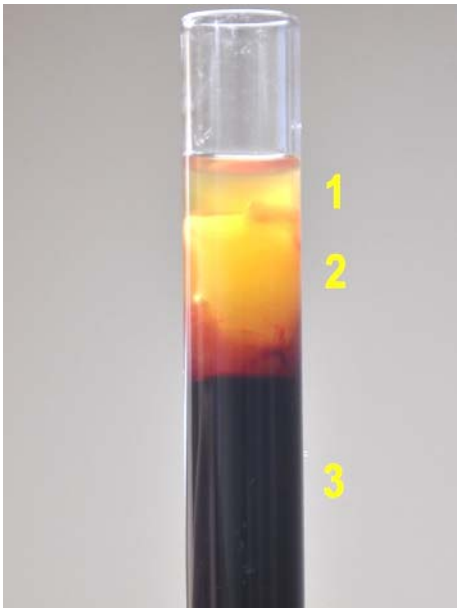
An advanced clinical, radiographic and laboratory study were carried out on the day of referral, later on the day 7 and 21 and at the end upon the consolidation of bone fragments.

The examination of patients was carried out in accordance with generally accepted Ukrainian standards for the examination of traumatic patients and in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

Clinical examination of patients was carried out according to the scheme, which included the acquisition and study of complaints, anamnesis vitae, anamnesis morbi, external examination of the face, oral cavity, teeth, palpation, evaluation of occlusion. The attention was paid to the increase of body temperature, the presence of the inflammation process, the prevalence and severity of its signs (swelling, tissue hyperemia, pain, exudation), mobility and degree of fragments shifting.

All 62 patients in the group have been already administered antibacterial drugs (lincomycin hydrochloride), local antiseptics and Ca-containing drugs (Ca-D3). On the day 7 of the study only 4 cases (6.5%) had a pronounced positive dynamic. Therefore, since the day 7 of the study, the rest of the 58 patients in the second group received the treatment complex developed by us, which was based on the literature and own data on early prediction of the delayed consolidation of the mandible bones, as a system for the prevention and treatment of this complication. According to the latter, our attention was focused on the following directions: firstly, a complete reposition of bone fragments; secondly – prevention and timely elimination of infectious-inflammatory complications by using short-term courses of antibiotic therapy in combination with immunomodulators; thirdly – increasing the activity of the antioxidant system; fourthly – stimulation of bone remodeling processes. Therefore, from the day 21 all patients with problematic consolidation of fragments were prescribed osteotropic drug Bivalos (strontium ranelate), 1 sachet once a day, for 14 days – antioxidant Mexidol – 100 mg/m twice a day to optimize the processes of osteogenesis, within 10-14 days – to eliminate the increase of processes of free radical lipid oxidation, human recombinant interleukin-2 (IL) – 2-3 intravenous administration of the drug for 48-72 hours (intravenous infusion of 500000 IU/24 hours/2 on the day 2-3/3 on the day 4-5) as an immunomodulating agent for correction of cytokines and immunoglobulins synthesis.

According to the research objectives these 58 patients with delayed consolidation of MF and lack of positive dynamics on the day 7 were divided into three groups (25, 25 and 8 patients respectively). 25 patients of the first group received a developed complex only. Patients of the second and third group received additional treatment according to the proposed methods: 25 patients in the first group were given fibrin-enriched platelets (iPRF) according to the developed methodology (Patent of Ukraine for Utility Model No. 100549). On the day 7 of the study, after antiseptic treatment of the oral cavity with a solution of 0.02% chlorhexidine bigluconate, injected under the mucous membrane along the MF fissure 1.0 ml of fibrin-enriched platelets was injected (Fig.).




**Notes:** 1 – PPP (platelet-poor plasma); 2 – L-PRF (Leucocyte and Platelet Rich Fibrin); 3 – RBC (red blood cells). Taking injectable iPRF is carried out via a syringe between layers 1 and 2.

**Distribution in fractions of patients venous blood after single centrifugation for 10.0-10.5 minutes**

In 8 patients of the second group an injection of 0.25 g recombinant morphogenetic protein (rhBMP-2) (Cowellmedi, South Korea) was used on the day 7 of the study in addition to the treatment-prophylactic complex developed by us.

The rhBMP-2 was created in South Korea by the method of drying morphogenetic protein of the second type. The development was approved by KFDA in 2010, being produced as the only osteoinductive osteoplastic material. CowellBMP contains 1 mg of BMP per g of powder (for comparison: 1 g of autobone contains 2 ng of BMP). It stimulates regeneration of bone tissue. BMP-2 is attached to the membrane of the stem cell and causes the expression of nucleus genes. Then BMP-2 migrates to the recipient zone. The growth factor of BMP-2, the Twist-2 transcription factor, and the VEGF growth factor contribute to the synthesis and secretion of the endogenous growth factor. Stimulates the proliferation of osteoblasts and their transition to osteocytes, fibroblasts in the dermis and keratinocytes in the skin, that is, the transcription factor Twist-2 provides regeneration of bone tissue and adjacent soft tissues.

The rhBMP-2 solution for injections was prepared according to the instructions, following the sterility requirements: with a disposable syringe, 0.2 ml of saline solution in a vial with 0.25 g of BMP powder was added until the complete dissolution, the resulting liquid was collected into the syringe.

After antiseptic irrigation of tunica mucosa of mouth with 0.02% of chlorhexidine bigluconate injected under the peri-osteum along the MF fissure, 0.2 ml of rhBMP-2 solution was injected once.

The examinations were carried out on a cone-beamed computerized tomograph Planmeca Promax 3D (Finland) with an X-ray emitter of 85 kV 5-7 mA on the day 7 and 21 of the study.

The images were stored in DCOM format and opened on the computer monitor in the Romexis Viewer. This program allowed to view images in any plane, to measure the bone density in units of Hounsfield (HU) on any part of the jaw. For this purpose the program measures the coefficient of X-ray radiation attenuation (absorption coefficient) that passed through the object. The denser the tissue, the more the X-ray beam is absorbed and attenuated, while passing through it. Accordingly, the higher is the attenuation coefficient and the HU value. The bone absorbs X-rays more intensely than other tissues and has the highest coefficient. The air virtually does not absorb and has the lowest absorption coefficient. The absorption coefficient of water is taken as 0. Therewith, the higher the coefficient of absorption of the tissue, the more it absorbs radiation, the less photons of radiation reaches the detector of the tomograph, and the more white it looks on the computer screen: the bone is the most white, the air is the darkest. Thus, the distinction between normal and pathological formations on a computer tomograph is carried out according to the gradations of transition from black to white (gradations of gray color). The evaluation of the density of jaw bone tissue was conducted by U. Lekholm and G. Zarb (1985) classifications, and by S. Mish (1990). Bone density of more than 850 units was considered as an intact dense bone, the values from 350 to 850 units – as a relatively intact, loose bone, and less than 350 Hounsfield units – local osteoporosis. To obtain data of the density of jaw bone tissue, after computer tomography of mandible performing and obtaining the image of the jaw on the monitor screen, the bone density measurement tool was activated by the mouse button and the data were received at three points, located on one section of the straight perpendicular line to the line of the fracture, moving away from the lower edge of the jaw by 1 cm, with a distance between the points of 0.5 cm. The measurements were measured on each of the fragments. Subsequently, the arithmetic mean was used.

Statistical processing of materials was carried out using standard methods of variation statistics using the STATISTIKA (ver. 6.1; Statsoft Inc., USA, No. AGAR 909E415822FA).

**RESULTS AND DISCUSSION**

It should be noted that all patients of all groups had a positive dynamic of clinical and laboratory parameters, but in the third group these results were the best. On the first day of referral, in 5 of 8 patients in the third group, a moderate swelling of the oral tunica mucosa in the area of MF fissure, unpleasant tensive sensations at the fracture site (as well as pain, heaviness, heartburn, etc.) were observed in all cases, a tight motion of fragments and functional impairments (difficult opening of the mouth, impossibility to bite off and chew solid food) were noted. The symptom of indirect load was positive in all patients of the subgroup.

Injections were painless and did not require additional analgesia; we did not observe any cases of reactive inflammation during the first 2-3 weeks after rhBMP-2 introduction. On the contrary, 4 out of 5 patients already on the day 3 after the administration of the drug noticed a decrease in swelling of oral tunica mucosa in the area of MF fissure and disappearance of subjective pain symptoms.

All patients in this subgroup on the day 14 of the study had no complaints of pain and discomfort in the MF area. At this stage of the study the symptom of indirect load was negative in all 8 patients. In all 8 (8/8) cases we observed a reparative reaction

according to the type of initially delayed adhesion, without the formation of a pronounced callus. It should be noted that in the second group, this type of reparative reaction occurred in 14 of 25 patients (66%), in the first group – in 3 of 25 patients (12%). The dynamics of the density of jaw bone tissue in the fracture zone in patients by groups is presented in Table.

**Dynamics of MBD in the MF zone in patients with delayed consolidation (M±m)**

| Subgroup | Values of the density of jaw bone tissue in units by Hounsfield | | |
|---|---|---|---|
| | 1st day | 7th day | 21st day |
| First | 571.0±48.9<br>p1-3=0.87 | 585.7±43.2<br>p1-3<0.005<br>p1=0.33 | 600.7±37.3<br>p1-3<0.005<br>p1=0.27<br>p2=0.04 |
| Second | 576.8±47.3<br>p1-2=0.71 | 588.5±43.9<br>p1-2=0.85<br>p1=0.43 | 610.7±33.4<br>p1-2=0.42<br>p1=0.09<br>p2=0.02 |
| Third | 574.3±24.3<br>p2-3=0.90 | 708.3±8.4<br>p2-3<0.005<br>p1<0.005 | 753.1±8.7<br>p2-3<0.005<br>p1<0.005<br>p2<0.005 |

**Notes:** p – difference between groups at this stage; p1 – difference in relation to the previous stage; p2 - difference between values on 1st and 21st day; p1-3; p1-2; p2-3 - difference between subgroups.

It is noteworthy that the bone tissue density in patients of three groups significantly increased on the day 21. However, in patients of the second group delayed contact osteogenesis was observed in 19 cases (63.3%), compared to 8 cases (26.7%) in the first group. As for the first group, the reparative reaction in most cases occurred with pronounced bone marrow formation – in 22 patients (73.3%) compared with 11 cases (36.7%) in the second group, in which iPRF was used.

However, additional inclusion in the treatment complex of recombinant morphogenetic protein showed better restoration of density of jaw bone in the MF zone compared to a similar scheme using iPRF. Thus, the use of rhBMP-2 in the complex therapy of delayed consolidation of MF promotes optimization of reparative osteogenesis and ensures its favorable course by the type of initially delayed adhesion. Taking into account the above, it is advisable to add injection of recombinant morphogenetic protein to the plan of treatment in patients with delayed consolidation of MF.

Summarizing, it should be determined that the use in the therapy of delayed consolidation of MF of the developed complex, which includes strontium ranelat (Bivalos), the drug of osteotropic action, antioxidant Mexidol, recombinant human IL-2 immunomodulator, and local administration of iPRF, containing numerous growth factors, along the fracture fissure or in more complex cases – of recombinant BMP-2, made it possible to achieve improvement of reparative processes in all 58 patients. It should be emphasized that in no case there was any need for additional surgical intervention for osteosynthesis or bone grafting.

**CONCLUSIONS**

1. The basic program on care of patients with a delayed consolidation of mandible fractures should affect all pathogenesis components of this complication: it should include osteotropic drugs, antioxidants and immunomodulators.
2. Involvement of fibrin-enriched platelets in the integrated therapy positively affects the quality of bone regenerate and treatment terms, ensuring the normalization of clinical and laboratory parameters up to the day 21. In patients of fibrin-enriched platelets group a delayed contact osteogenesis was more frequent – in 19 cases (63.3%), compared to 8 cases (26.7%) in the first subgroup, at the same time in most cases without fibrin-enriched platelets use, the restoration took place with pronounced callus formation – in 22 patients (73.3%), and in the group of patients receiving fibrin-enriched platelets the expressed periosseous reaction was observed only in 11 patients (36.7%).
3. The best optimization of reparative osteogenesis in the complex therapy of delayed consolidation of mandible fractures is facilitated by the additional injection of recombinant morphogenetic protein – 2.

This tactic allowed to ensure its favorable course by the type of initially delayed adhesion in all patients (8 out of 8).

Conflict of interests. The authors declare no conflict of interest.

## REFERENCES


1. Garrison KR, Shemit I, Donell S, Ryder JJ, Mugford M, Harvey I, et al. Bone morphogenetic protein (BMP) for fracture healing in adults. Cochrane Database Syst Rev. 2010 Jun;16(6):CD006950. doi: https://doi.org/10.002/14651858. CD006950.pub.2
2. Emara KM, Diab RA, Emara AK. Recent biological trends in management of fracture non-union. World J Orthop. 2015 Sep;6(8):623-8. doi: https://doi.org/10.5312/wjo.v6.i8.623
3. Cameron JA, Milner DJ, Lee JS, Cheng J, Fang NX, Jasiuk IM. Employing the biology of successful fracture repair to heal critical size bone. Curr Top Microbiol Immunol. 2013;367:113-32. doi: https://doi.org/10.1007/82_2012_291.
4. Gaihre B, Uswatta S, Jayasuriya AC. Reconstruction of Craniomaxillofacial Bone Defects Using Tissue-Engineering Strategies with Injectable and Non-Injectable Scaffolds. J Funct Biomater. 2017;8(4):1-19. doi: https://doi.org/10.3390/jfb8040049
5. Gudaryan OO, Idashkina NG, Nekhanevich ZM. Effectiveness of morphogenetic protein rhBMP-2 use in atypical third mandibular molars extraction. Medicni perspektivi. 2020;25(2):137-144 doi: https://doi.org/10.26641/2307-0404.2020.2.206789
6. Hankenson KD, Zimmerman G, Marcucio R. Biological perspectives of delayed fracture healing. Injury. 2014;45(02):8-15. doi: https://doi.org/10.1016/j.injury.2014.04.003
7. Herford AS. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillofacial trauma. Chin J Traumatolog. 2017;20(1):1-3. doi: https://doi.org/10.1016/j.cjtee.2016.05.004
8. Herford AS, Miller M, Signorino F. Maxillofacial Defects and the Use of Growth Factors. Oral Maxillofacial Surg Clinics North America. 2017;29(1):75-88. doi: https://doi.org/10.1016/j.coms.2016.08.006
9. Hurell MJL, David MC, Batstone MD. Patient compliance and mandible fractures: a prospective study. Int J Maxillofac Surg. 2019. pii: S0901-5027(18)30452-1. doi: https://doi.org/10.1016/j.ijom.2018.11.011
10. Huang W, Hasegawa T, Imai Y, Takeda D, Akashi M, Komori T. Low-intensity pulsed ultrasound enhances bone morphogenetic protein expression of human mandibular fracture haematoma-derived cells. Int J Oral Maxillofac Surg. 2015;44(7):929-35. doi: https://doi.org/10.1016/j.ijom.2015.03.001
11. Pickrell BB, Serebrakian AT, Maricevich RS. Mandible Fractures. Semin Plast Surg. 2017;31(2):100-7. doi: https://doi.org/10.1055/s-0037-1601374
12. Rouwkema J, Rivron NC, Blitterswijk C. Vascularization in tissue engineering. Trends Biotech. 2008;26:434–441. doi: https://doi.org/10.1016/j.tibtech.2008.04.009
13. Sánchez-Duffhuesa G, Hiepen C, Knaus P, Dijkea P. Bone morphogenetic protein signaling in bone homeostasis. Bone. 2015;80:43-59. doi: https://doi.org/10.1016/j.coms.2016.08.006
14. Abou Neel EA, Chrzanowski W, Salih VM, Kim HW, Knowles JC. Tissue engineering in dentistry. J Dent. 2014 Aug;42(8):915-28. doi: https://doi.org/10.1016/j.jdent.2014.05.008


## СПИСОК ЛІТЕРАТУРИ


1. Bone morphogenetic protein (BMP) for fracture healing in adults / K. R. Garrison et al. *Cochrane Database Syst Rev.* 2010. Jun. (Vol. 16, No. 6). P. CD006950. DOI: https://doi.org/10.002/14651858. CD006950.pub.2
2. Emara K. M. , Diab R. A., Emara A. K. Recent biological trends in management of fracture non-union. *World J Orthop*. 2015. Sep. (Vol. 6, No. 8). P. 623-628. DOI: https://doi.org/10.5312/wjo.v6.i8.623
3. Employing the biology of successful fracture repair to heal critical size bone / J. A. Cameron et al. *Curr Top Microbiol Immunol.* 2013. Vol. 367. P. 113-132. DOI: https://doi.org/10.1007/82_2012_291.
4. Gaihre B., Uswatta S., Jayasuriya A. C. Reconstruction of Craniomaxillofacial Bone Defects Using Tissue-Engineering Strategies with Injectable and Non-Injectable Scaffolds. *J Funct Biomater*. 2017. Vol. 8, No. 4. P. 1-19. DOI: https://doi.org/10.3390/jfb8040049
5. Gudaryan O. O., Idashkina N. G., Nekhanevich Z. M. Effectiveness of morphogenetic protein rhBMP-2 use in atypical third mandibular molars extraction. *Medicni perspektivi*. 2020. Vol. 25, No. 2. P. 137-144. DOI: https://doi.org/10.26641/2307-0404.2020.2.206789
6. Hankenson K. D., Zimmerman G., Marcucio R. Biological perspectives of delayed fracture healing. *Injury.* 2014. Vol. 45, No. 02. P. 8-15. DOI: https://doi.org/10.1016/j.injury.2014.04.003
7. Herford A. S. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillofacial trauma. *Chin J Traumatolog*. 2017. Vol. 20, No. 1. P. 1-3. DOI: https://doi.org/10.1016/j.cjtee.2016.05.004
8. Herford A. S., Miller M., Signorino F. Maxillofacial Defects and the Use of Growth Factors. *Oral Maxillofacial Surg Clinics North America.* 2017. Vol. 29, No. 1. P. 75-88. DOI: https://doi.org/10.1016/j.coms.2016.08.006

9. Hurell M. J. L., David .M. C., Batstone M. D. Patient compliance and mandible fractures: a prospective study. *Int J Maxillofac Surg*. 2019. pii: S0901-5027(18)30452-1. DOI: https://doi.org/10.1016/j.ijom.2018.11.011

10. Low-intensity pulsed ultrasound enhances bone morphogenetic protein expression of human mandibular fracture haematoma-derived cells / W. Huang et al. *Int J Oral Maxillofac Surg.* 2015. Vol. 44, No. 7. P. 929-35. DOI: https://doi.org/10.1016/j.ijom.2015.03.001

11. Pickrell B. B., Serebrakian A. T., Maricevich R. S. Mandible Fractures. *Semin Plast Surg*. 2017. Vol. 31, No. 2. P. 100-107. DOI: https://doi.org/10.1055/s-0037-1601374

12. Rouwkema J., Rivron N. C., van Blitterswijk C. Vascularization in tissue engineering. *Trends Biotech*. 2008. Vol. 26. P. 434-441.
DOI: https://doi.org/10.1016/j.tibtech.2008.04.009

13. Sánchez-Duffhuesa G., Hiepen C., Knaus P., Dijkea P. Bone morphogenetic protein signaling in bone homeostasis. *Bone*. 2015. Vol. 80. P. 43-59. DOI: https://doi.org/10.1016/j.coms.2016.08.006

14. Tissue engineering in dentistry / E. A. Abou Neel et al. *J Dent.* 2014. Aug. (Vol. 42, No. 8). P. 915-28. DOI: https://doi.org/10.1016/j.jdent.2014.05.008

Стаття надійшла до редакції
24.12.2020