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Morphometric indicators of wound bone tissue condition after surgical treatment of spontaneous periodontitis accompanied by different functional state of organism reactivity

Yu. Yu. Yarov*

Donetsk National Medical University, Kropyvnytskyi, Ukraine

In periodontal surgery, advanced technologies such as the use of platelet-enriched plasma, the technique of directed tissue regeneration, applying various osteoplastic materials are widely spread. Despite the undoubted achievements, there is a risk of postoperative complications.

The aim of the work was to study the intensity and duration of the wound healing phases after surgical treatment of spontaneous periodontitis accompanied by normo-, hyper- or hyporeactivity of the body by bone morphometry.

Materials and methods. Wistar rats were selected for the study – 90 nonlinear white adult male rats weighing 270 ± 58 grams, aged 11–12 months with spontaneous periodontitis. The animals were divided into three equal groups depending on the condition of their organism reactivity. All the animals underwent surgery on the periodontium: one half of the animals in each of the three groups underwent flap operations, the other – flap operations with osteoplasty (Kolapan-L, Hypro-sorb F). The specific weight of microhemocirculatory bed, connective tissue and bone granulation tissue, bone trabeculae, bone marrow cavities, polymorphonuclear leukocytes, lymphocytes, macrophages, plasma cells was studied by a morphometric method.

Results. Morphometric study of bone wound preparations from animals with spontaneous periodontitis accompanied by normoreactivity of the body has allowed to identify the following phases of healing during the wound process: degenerative-inflammatory changes (the 10th day), an increase in reparative processes (the 20th day) and active regeneration (the 30th day). In cases of hyper- and hyporeactivity, the intensity and duration of the wound healing phases differed. In case of hyperreaction, the granulocyte-macrophage reaction was more expressed and lasted longer until the 20th day, therefore later, only on the 30th day, the signs of regeneration could be observed. In case of hyporeaction, the granulocyte reaction appeared later (only on the 20th day) and lasted longer, signs of active regeneration were noticed later, on the 30th day. The identified patterns occurred regardless of the absence or presence of osteoplastic material in a wound.

Conclusions. In case of normoreactivity, the intensity and timing of the wound process phases were optimal. In case of impaired (hyper- and hypo-) reactions, altered intensity of the cellular phase (increased or decreased) and terms (accelerated or slowed down) resulted in delayed bone wound healing, that is, a complicated course was observed. It justifies the feasibility and necessity of developing methods of targeted drug correction for transforming the wound process phases with impaired body reactivity into those that are typical of normoreaction.

Key words: reactivity of organism, spontaneous periodontitis, periodontal surgery, bone wound, bone morphology.

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***E-mail:** Kaf.stomatologii2@ukr.net

Морфометричні показники стану кісткової тканини рани після хірургічного лікування при спонтанному пародонтиті на тлі різного функціонального стану реактивності організму

Ю. Ю. Яров

У пародонтальній хірургії впроваджують передові технології, як-от використання збагаченої тромбоцитами плазми, техніка спрямованої регенерації тканин, використання різних остеопластичних матеріалів. Незважаючи на безсумнівні досягнення, залишається ризик виникнення післяопераційних ускладнень.

Мета роботи – вивчити інтенсивність і тривалість фаз перебігу загоєння рани після хірургічного лікування при спонтанному пародонтиті на тлі нормо-, гіпер- і гіпореактивності організму шляхом аналізу морфометрії кісткової тканини.

Матеріали та методи. Для дослідження обрали щурів породи Wistar – 90 нелінійних білих статевозрілих самців масою 270 ± 58 г, віком 11–12 місяців зі спонтанним пародонтитом. Тварин поділили на три групи (по 30 особин) залежно від стану реактивності організму. Всім тваринам здійснили хірургічне втручання на пародонті: одній половині тварин кожної з груп виконували клаптеву операцію, іншій – клаптеву операцію з остеопластикою (Колапан-Л, Hypro-sorb F). Морфометричним методом вивчали питому вагу мікрогемоциркуляторного русла, сполучнотканинної та кісткової грануляційної тканини, кісткових балок, кістковомозкових порожнин, поліморфноядерних лейкоцитів, лімфоцитів, макрофагів, плазмоцитів.

Результати. Морфометричне дослідження препаратів кісткової рани у тварин зі спонтанним пародонтитом при нормореактивності організму дало змогу визначити фази загоєння під час ранового процесу: дегенеративно-запальних змін (10 доба), наростання репаративних процесів (20 доба) та активної регенерації (30 доба). При гіпер- та гіпореактивності інтенсивність і тривалість фаз загоєння рани відрізнялися. У разі гіперреакції гранулоцитарно-макрофагальна реакція більш виражена, тривала понад 20 діб, і тому пізніше (на 30 добу) з'явилися ознаки регенерації. У разі гіпореакції гранулоцитарна реакція наставала пізніше (на 20 добу) і тривала довше, ознаки активної регенерації з'являлися пізніше – на 30 добу. Ці закономірності спостерігали незалежно від наявності чи відсутності остеопластичного матеріалу в рані.

Висновки. При нормореактивності інтенсивність і терміни фаз ранового процесу є оптимальними. При порушеній (гіпер-, гіпо-) реакції визначають зміни інтенсивності клітинної фази (підвищена або знижена) та термінів (прискорені або уповіль-

Ключові слова: реактивність організму, спонтанний пародонтит, пародонтальна хірургія, кісткова рана, морфометрія кісткової тканини.

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нені), що спричиняють відтерміноване загоєння кісткової рани, тобто ускладнений перебіг. Це обґрунтовує доцільність розроблення методів спрямованої медикаментозної корекції з приведенням фаз ранового процесу при порушеній реактивності організму до таких при нормореакції.

According to modern ideas, the treatment of generalized periodontitis is based on the principles of an integrated approach, which includes the use of therapeutic, surgical, orthopedic, orthodontic, physiotherapy interventions, general and local medications [1–5]. For treatment of generalized periodontitis of II, III degree of severity, surgical methods are the main ones [6].

Periodontal surgery has an etiotropic and symptomatic focus and aims at stopping the further development of the inflammatory-destructive process and restoring the periodontal structure and function. Data on the use of various osteoplastic materials and techniques of targeted tissue regeneration are highlighted. It has been proved that the use of platelet-enriched fibrin in the complex treatment for patients with generalized periodontitis of II–III degrees improved the postoperative course and stimulated regenerative processes [7].

Various osteoplastic materials have been widely used in periodontal surgery: synthetic calcium-phosphate, autogenous bone grafts, allogeneic bone, combined plastic materials, membranes for targeted bone regeneration, bioactive agents – bone growth factors, xenotransplants. The use of osteoplastic materials optimizes the conditions for the alveolar process bone tissue restoration, preventing epithelial vegetation of the gingival margin deep towards the apical part of the tooth root [8,9]. Positive results and high efficiency of periodontal surgical treatment consisting in stabilization of the process at the stage of severe tissue destruction, have been achieved not only due to the surgery, but also largely depended on heredity and consistency between physicians of all specialties involved in the treatment of patients, as well as on a course of medical correction, volume and tactics of surgery and postoperative rehabilitation measures [10–12].

However, there is always the risk of postoperative complications [13,14]. This called for further research in this direction with the aim of finding ways to optimize the interventions undertaken by increasing efficiency of pathogenetically targeted drug therapy. It has been proven that the state of body reactivity determines an outcome of post-myocardial infarction healing. In hyper- and hyporeactivity, healing after myocardial infarction is complicated by the damaged zone state (phases of cellular reactions are disturbed) and delayed. In case of normoreaction, the course of myocardial infarction is uncomplicated and characterized by adequate phases of the wound process and normal healing time [15]. Therefore, it is promising to use the principle of optimal management in the drug therapy of patients with generalized periodontitis, namely, an effect on complicated forms in order to bring the disease course closer to uncomplicated one.

Aim

The aim of this study was to examine the intensity and duration of the wound healing phases in the alveolar bone after surgical treatment with or without osteoplasty in case of spontaneous periodontitis accompanied by normo-, hyper- or hyporeactivity of the body by morphometric assessment of the correlation between tissues, bone trabeculae, bone marrow cavities, polymorphonuclear leukocytes, lymphocytes, macrophages and plasma cells.

Materials and methods

Wistar rats – 90 nonlinear white adult male rats weighing 270 ± 58 grams, aged 11–12 months, with spontaneous periodontitis were selected as experimental animals for this morphological study. The animals were kept in standard vivarium conditions. The choice of the study object was attributable to traditional laboratory animals (rats) with bone tissue similar to human bone tissue. The animals were divided into three equal groups depending on the condition of organism reactivity. In the first group, drugs that disrupt the organism reactivity were not used (normoreactivity of the organism). In this case, "placebo" animals were injected with saline. In the second group, immunostimulant pyrogenal at a dose of 10 μg/kg/day was injected intramuscularly to the animals, in that way, the condition of organism hyperreactivity was simulated. The animals of the third group received immunosuppressant azathioprine at a dose of 1.5 mg/kg/day enterally according to the scheme (the condition of organism hyporeactivity was simulated). The drugs were administered for a month – for the first 7 days daily, then – every 4 days. The choice of a body reactivity model was determined by the fact that, according to the author, the characteristic changes in the reactivity state were confirmed by the dynamics of adrenocorticotropic hormone, adrenaline, cortisol contents and index of blood leukocyte shift [15]. The periodontal tissues condition was evaluated according to generally accepted clinical indicators and periodontal indices. After modeling the organism reactivity, all the animals with spontaneous periodontitis underwent careful instrumental removal of soft and hard supragingival and subgingival dental deposits, drug treatment by irrigating the oral cavity with "Parodontax" rinse. Then, all the animals were subjected to a surgery on the periodontium: one half of the animals in each of the three groups underwent flap surgery according to Cieszyn-Widman-Neumann, the other – flap surgery with osteoplasty. Colapan-L and Hypro-sorb F were used as osteoplastic materials. Colapan-L is a drug for bone regeneration consisting of artificial hydroxyapatite, collagen and lincomycin. Hypro-sorb F is an absorbable bilayer collagen membrane made of highly purified collagen (99.9 %).

For the morphological study, the area of the alveolar bone adjacent to a surgical wound was used. Extraction of animal bone fragments was performed after sequential withdrawal of 5 animals of each group from the experiment by overdose of inhaled narcotic analgesic on the 10th, 20th and 30th day. Bone tissue was fixed for 24 hours in 10 % buffered formalin solution (pH 7.0). Then, it was decalcified in EDTA solution in a thermostat at 56 °C for 5 days. Decalcified bone was embedded in paraffin at a temperature not exceeding 60 °C. The sections were prepared with a rotary microtome Microm HM325 (Carl Zeiss, Germany) and

Table 1. Morphometric parameters of bone tissue after surgical treatment without osteoplasty in cases of body normo-, hyper- and hyporeactivity, M ± SE

Groups	Day	Specific weight (%)					
		MHCB	CTBGT	BT	BMC	PMNLs	L, M, P
Normoreaction	10	9.52 ± 1.03	12.59 ± 2.23	2.07 ± 0.64	0.50 ± 0.12	39.16 ± 3.02	35.49 ± 3.01
	20	12.95 ± 1.80	19.47 ± 3.15	16.01 ± 2.23	4.50 ± 1.42	17.03 ± 1.63	19.04 ± 1.01
	30	5.06 ± 0.54	30.46 ± 4.82	32.63 ± 2.26	10.89 ± 1.00	12.96 ± 1.01	17.54 ± 1.04
Hyperreaction	10	3.36 ± 0.65	3.58 ± 0.44*	0.82 ± 0.63	0.36 ± 0.02	48.23 ± 3.34*	43.65 ± 4.05*
	20	7.12 ± 1.08*	15.22 ± 2.88	5.67 ± 0.66*	1.98 ± 0.14*	37.34 ± 3.08*	32.67 ± 2.86*
	30	11.86 ± 1.86*	24.32 ± 3.45*	15.65 ± 2.08*	4.63 ± 0.46*	17.86 ± 1.64*	25.68 ± 1.34*
Hyporeaction	10	3.12 ± 1.43*	3.28 ± 0.38*	0.74 ± 0.54*	0.32 ± 0.08	25.64 ± 1.34*	22.45 ± 1.08*
	20	6.09 ± 1.03*	12.34 ± 1.68*	4.21 ± 0.32*	0.98 ± 0.09*	27.71 ± 1.42*	28.23 ± 1.75*
	30	11.44 ± 1.34*	20.87 ± 2.61*	14.65 ± 1.96*	3.78 ± 0.67*	19.34 ± 1.12*	22.45 ± 1.67*

*: $p < 0.05$ in relation to the corresponding values in case of body normoreactivity.

placed on slides SuperFrost (Menzel, Germany) and stained with hematoxylin-eosin according to standard methods. The studies of the drugs were performed in transmitted light with the help of a microscope "Axiostar" (Carl Zeiss, Germany). The morphometric method was used to detect specific weight of microhemocirculatory bed (MHCB), connective tissue and bone granulation tissue (CTBGT), bone trabeculae (BT), bone marrow cavities (BMC), polymorphonuclear leukocytes (PMNLs), plasma cells (P). Measurements were performed by the Glagolev point-count method using an eyepiece measuring grid in 35 fields of view at a step of 30 μm. The experimental studies took into account the recommendations given in the Regulation "General Ethical Principles of Animal Experimentation", approved by the First National Congress on Bioethics on September 20, 2001 (Kyiv, Ukraine) and the regulations of "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Strasbourg, 1985). Morphometric studies were carried out at Donetsk National Medical University, Department of Pathological Anatomy, Forensic Medicine and Histology.

The obtained digital data were processed by variational statistical methods of analysis using standard Microsoft Excel software IBM PC. For each sample population of observations (n), the arithmetic mean (M), standard error of the mean (SE), standard deviation (SD), 95 % confidence interval of the true mean was calculated using the Student's t-test.

Results

The results of the study on reparative processes in the bone wound after surgical treatment without osteoplasty in animals with spontaneous periodontitis and normoreactivity are presented in *Table 1*. As can be seen from this table, an active degenerative-inflammatory reaction could be observed for the first 10 days in the bone wound, which was characterized by a large number of cells (in total, a proportion of PMNLs, lymphocytes, macrophages and plasma cells was almost 75 %) in the specimens.

Elements of the MHCB and CTBGT had 3.4 times less specific weight. BT (2.07 ± 3.14 %) and BTCs (0.50 ± 0.12 %) were revealed in limited numbers. On the 20th day, the correlation between morphometric parameters was changed: a percentage of cells was 2.01 times lower, MHCB and CTBGT were 1.36 and 1.55 times ($p < 0.05$) higher, respectively. In addition, there was an increase in the number of BT (7.73 times, $p < 0.05$) and BTCs (9.00 times, $p < 0.05$) in the specimens. This morphological picture indicated the beginning of active regenerative process development in the bone wound. On the 30th day of observation, the predominant morphometric parameters in the bone wound were CTBGT, BT and BTCs (their proportion in relation to the number was 73.98 %) indicating an active course of the healing process. Thus, morphometric examination of bone wound specimens after surgical treatment without osteoplasty from animals with spontaneous periodontitis and body normoreactivity allowed to identify the following periods of cellular reactions during the wound process: the period of degenerative-inflammatory changes (the 10th day), the period of reparative processes (the 20th day) and the period of active regeneration (the 30th day).

The results of the study on reparative processes in the bone wound after surgical treatment with osteoplasty ("Colapan" with osteoconductive properties was used as an osteoplastic material for half of the animals, "Hypro-sorb F" including osteoinductor was used for the other half) in animals with spontaneous periodontitis accompanied by body normoreactivity are shown in *Table 2*. During that initial ten-day period, there was an active degenerative-inflammatory reaction, which was characterized by a large number of cells in the specimens (the total percentage of PMNLs, lymphocytes, macrophages and plasma cells was almost 61 %). A proportion of the MHCB and CTBGT elements was 2.23 times less ($p < 0.05$). BT (6.41 ± 1.56 %) and BTCs (2.70 ± 0.60 %) were less numerous. However, one should pay attention to their significantly higher number than after surgery without osteoplasty, 3.09 and 5.4 times ($p < 0.05$), respectively.

On the 20th day, the correlation between morphometric parameters was changed: the total proportion of cells was 1.96 times decreased, MHCB and CTBGT were increased by 1.17 and 1.76 times, respectively ($p < 0.05$). At the same time, their significant increase by 1.29 and 1.18 times, respectively, compared with those after surgical treatment without osteoplasty, drew the attention. This morphological picture indicated a more pronounced beginning of active regenerative process development in the bone wound with osteoplastic material. On the 30th day of observation, the predominant morphometric parameters in the bone wound were CTBGT, BT and BMCs (their percentage in relation to the number was 80.46 %, which was 6.48 % more than the value without osteoplasty) indicating an active course of the healing process. Thus, morphometric study of bone

Table 2. Morphometric parameters of bone tissue after surgical treatment with osteoplasty in cases of body normo-, hyper- and hyporeactivity, M ± SE

Groups	Day	Specific weight (%)					
		MHCB	CTBGT	BT	BMC	PMNL	L, M, P
Normoreaction	10	6.12 ± 1.01	21.15 ± 4.00	6.41 ± 1.56	2.70 ± 0.60	31.09 ± 4.74	29.86 ± 3.30
	20	7.18 ± 1.24	37.38 ± 5.60	20.78 ± 2.06	5.32 ± 0.73	14.31 ± 4.29	16.71 ± 2.35
	30	2.32 ± 0.51	30.32 ± 3.24	35.82 ± 3.47	14.32 ± 3.27	2.38 ± 1.07	14.32 ± 1.36
Hyperreaction	10	4.72 ± 0.65*	5.12 ± 0.82*	1.44 ± 0.63*	0.96 ± 0.34*	49.97 ± 5.08*	44.46 ± 4.88*
	20	5.85 ± 1.11	16.12 ± 2.72*	5.98 ± 0.68*	2.01 ± 0.20*	39.03 ± 3.16*	33.31 ± 3.03*
	30	12.08 ± 1.88*	25.54 ± 3.52	16.85 ± 2.10*	4.95 ± 0.47*	18.06 ± 1.70*	26.42 ± 1.38*
Hyporeaction	10	3.82 ± 1.45	6.92 ± 0.43 *	1.28 ± 0.62*	0.68 ± 0.10*	27.74 ± 1.40	24.85 ± 1.10
	20	6.99 ± 1.08	18.02 ± 1.78 *	8.54 ± 0.92*	2.04 ± 0.12*	30.01 ± 1.51*	29.11 ± 1.82*
	30	8.11 ± 1.00*	26.72 ± 2.93	24.02 ± 2.06*	6.23 ± 0.99*	11.93 ± 1.10*	12.22 ± 1.08*

*: $p < 0.05$ in relation to the corresponding values in case of body normoreactivity.

wound specimens after surgical treatment with osteoplasty from animals with spontaneous periodontitis accompanied by body normoreactivity showed that the use of osteoplastic material contributed to more active development of reparative processes in the wound, acting as a local stimulator. The wound process phases remained the same as those without using the osteoplastic material.

A synthesis of the results obtained has shown that the intensity and timing of the wound healing phases were a consequence of the normoreactive response to damage with the synchronization of necrotic and reparative processes. This, ultimately, provided conditions for normal uncomplicated osteoregeneration of the alveolar bone, as evidenced by morphometric studies on the proportion of MHCB, CTBGT, BT and BMCs, polymorphonuclear leukocytes, lymphocytes, macrophages and plasma cells.

The results of the study on reparative processes in the bone wound after surgery without osteoplasty in animals with spontaneous periodontitis accompanied by body hyperreactivity are demonstrated in *Table 1*. During the first 10 days, there was a pronounced degenerative-inflammatory reaction, characterized by a significant predominance of large cells, the percentage of PMNLs, lymphocytes, macrophages and plasma cells was almost 91.88 %, which was 1.22 times more than the corresponding value in cases of normoreaction, $p < 0.05$). All the other morphometric parameters were observed in the specimens only. On the 20th day, despite a slight decrease, there was a high specific weight of PMNLs, lymphocytes, macrophages and plasma cells. There was a significant increase in MHCB, CTBGT in the specimens compared to those on day 10. It should be taken into consideration that the content of these morphometric parameters in this period was significantly 1.82 and 1.28 times ($p < 0.05$) lower, respectively, than those of normoreactivity. This morphological picture indicated a more pronounced and prolonged inflammatory stage of bone wound healing in case of body hyperreactivity. On the 30th day of observation, the correlation between inflammatory and regenerative elements was equalized due to a significant decrease in the percentage of PMNLs, lymphocytes, macrophages, plasma cells and an increase in the amount of MHCB, CTBGT as well as a number of BN and BMCs. It is important that the number of BT and BMCs was significantly smaller compared to that of normoreactivity, 2.08 and 2.35 times less ($p < 0.05$), respectively, characterizing only the beginning of the healing process. Thus, morphometric examination of bone wound specimens after surgical treatment without osteoplasty in animals with spontaneous periodontitis accompanied by body hyperreactivity was delayed because the cellular inflammatory response was significantly more pronounced and lasted longer, the signs of active osteoregeneration were observed later.

The results of the study on reparative processes in the bone wound after surgical treatment using osteoplastic material “Kolapan” with osteoconductive properties in animals with spontaneous periodontitis accompanied by body hyperreactivity are shown in *Table 2*. During the first 10 days, there was a pronounced degenerative-inflammatory reaction which was characterized by a large number of cells (in total, the percentage of PMNLs, lymphocytes, macrophages and plasma cells was almost 94.46 %, which was 1.55 times more than the corresponding value in case of normoreaction, $p < 0.05$ and compared with the values after surgical treatment without osteoplasty, $p > 0.05$). All the other morphometric parameters were observed in the specimens in limited quantities. On the 20th day, despite a slight decrease, there was a high specific content of PMNLs, lymphocytes, macrophages and plasma cells. There was a significant increase in the proportion of MHCB and CTBGT in the specimens in comparison with that on day 10. It should be noted that these morphometric parameters in this period were 1.23 and 2.32 times significantly lower, respectively, than those of normoreactivity and after surgical treatment without osteoplasty ($p > 0.05$). The presented morphological picture showed a more pronounced and prolonged inflammatory stage of bone wound healing accompanied by body hyperreactivity, regardless of the absence or presence of osteoplastic material in the wound. On day 30 of the observation, the correlation between inflammatory and regenerative elements was equalized due to a significant decrease in the percentage of PMNLs, lymphocytes, macrophages, plasma cells and an increase in MHCB, CTBGT, BT and BMCs. Importantly, the BT and BMC contents were significantly 2.12 and 2.89 times less ($p < 0.05$), respectively, compared to that of normoreactivity indicating only the beginning of bone wound healing. Therefore, morphometric examination of bone wound specimens after surgical treatment with osteoplasty from animals with spontaneous periodontitis was accompanied by body hyperreactivity and delayed because the cellular inflammatory response was pronounced and lasted longer, but later on, there were signs of active osteoregeneration. This morphological picture occurred regardless of the osteoplastic material absence or presence in the wound.

Thus, the study on morphometric parameters of bone tissue after surgery in animals with spontaneous

periodontitis and body hyperreactivity allowed to identify the same periods of osteoregeneration as in the case of normoreaction. However, the intensity and duration of the wound healing phases differed from those, which were typical for body normoreactivity: granulocyte-macrophage reaction was more pronounced and lasted longer until the 20th day, so the signs of regeneration were later, only on the 30th day. It demonstrated that postoperative wound healing in animals with increased body reactivity was complicated, as evidenced by morphometric studies of the correlation between MHCB, CTBGT, BT and BMCs, lymphocysts and PMNLs.

The results of the study on reparative processes in the bone wound after surgical treatment without osteoplasty in animals with spontaneous periodontitis accompanied by body hyporeactivity are demonstrated in *Table 1*. During the first 10 days, there was a weak degenerative-inflammatory reaction, characterized by significantly lower number of macrophages and plasma cells in the specimens, in comparison with that of normoreactivity (the total number of PMNLs, lymphocytes, macrophages and plasma cells was 1.55 times less than the corresponding value typical for normoreaction, $p < 0.05$). All the other morphometric parameters were observed in the specimens in limited numbers. On day 20, despite a slight increase, there were relatively low proportions of PMNLs, lymphocytes, macrophages and plasma cells in comparison with their maximum values in case of normoreactivity. There was a significant increase in MHCB, CTBGT in the specimens as compared to the 10th day. It is necessary to consider that the contents of these morphometric parameters in this period were significantly 2.12 and 1.58 times ($p < 0.05$) lower, respectively, than those of normoreactivity. This morphological picture displayed a less pronounced and prolonged inflammatory stage of bone wound healing accompanied by body hyporeactivity. On observational day 30, the correlation between inflammatory and regenerative elements was equalized due to a significant decrease in the percentage of PMNLs, lymphocytes, macrophages, plasma cells and an increase in the number of MHCB, CTBGT, BN and BMCs. It is noteworthy that the numbers of BT and BMCs were significantly 2.22 and 2.88 times less ($p < 0.05$) lower, respectively, compared to those of normoreactivity, characterizing only the beginning of healing processes development. So, morphometric study of bone wound specimens from animals with spontaneous periodontitis accompanied by body hyporeactivity has shown a delayed bone wound healing because the inflammatory cell response occurred later and lasted longer, therefore, the signs of active osteoregeneration were observed later.

The results of the study on reparative processes in the bone wound after surgical treatment with osteoplasty in animals with spontaneous periodontitis accompanied by hyporeactivity are shown in *Table 2*. During the first 10 days, there was a relatively less pronounced degenerative-inflammatory reaction, which was characterized by a lower number of macrophages and plasma cells in the specimens compared with that of normoreactivity (the total portion of PMNLs, lymphocytes, macrophages and plasma cells was 1.16 times less than the corresponding value in normoreaction, $p > 0.05$). At the same time, a more expressed cellular reaction was noticeable in the wound after using osteoplastic inducer material in comparison with that without using osteoplasty. All the other morphometric parameters were observed in the specimens to a small extent. On day 20, the cellular morphological picture in the wound with osteoplastic material corresponded to that typical for normoreaction on the 10th day, namely, there was an active degenerative-inflammatory reaction, which was characterized by a large number of cells in the specimens, macrophages and plasma cells accounted for almost 60 %. There was a significant increase in the proportion of MHCB, CTBGT, BN and BMCs ($p < 0.05$) in the specimens compared with that on day 10. Although it is worth noting that the content of these morphometric parameters in this period was significantly lower than that of normoreactivity ($p < 0.05$). This morphological picture indicated a less pronounced and prolonged inflammatory stage of bone wound healing in body hyporeactivity compared to that of normoreaction. However, the inflammatory cellular response after using osteoplastic inducer material was more active in comparison with that after surgical treatment without using osteoplastic material. On the observational day 30, the correlation between morphometric parameters was changed: the percentage of cells was 2.45 times decreased, MHCB and CTBGT – 1.16 and 1.48 times increased ($p < 0.05$), respectively. In addition, there was an increase in the content of BT (2.81 times, $p < 0.05$) and BMCs (3.05 times, $p < 0.05$) in the specimens. This morphological picture showed a more active development of regenerative processes in the bone wound after surgical treatment using osteoplastic material with a regeneration inducer in comparison with that without osteoplasty. Though it is worth noting that the speed of regenerative reactions was still lower than that of normoreactivity, which required an additional drug correction.

Thus, the study on morphometric parameters of bone tissue after surgical treatment in animals with spontaneous periodontitis with body hyporeactivity has allowed to identify the same periods of osteoregeneration as with normo- and hyperreaction. However, the intensity and duration of the bone wound healing phases differed from those of body normoreactivity: granulocyte reaction occurred later (only on the 20th day) and lasted longer, signs of active regeneration appeared later, on the 30th day. This indicates that postoperative wound healing in animals with body hyperreactivity was complicated as evidenced by morphometric studies on the proportion of MHCB, CTBGT, BT and BMCs, lymphocysts and PMNLs.

Discussion

Previous studies have shown the dependence of the wound healing process on the condition of organism reactivity. It has been proven that the wound healing process during myocardial infarction was determined by the organism reactivity status, namely, the state of the damaged area and the healing time. When an organism is normoreactive, the intensity and duration of wound healing phases provided conditions for normal, uncomplicated healing after myocardial infarction. When the body reactivity was impaired, post-infarction healing was delayed with a violation of phases, which was determined morphologically, that is, it was complicated. It has been proposed to apply the principle of optimal management, in particular, effects of drug therapy

on complicated forms, in order to bring the disease course closer to uncomplicated one based on the state damage zones, regulatory systems, and phases of development. It requires study on the specifics of the wound process course in inflammatory-destructive periodontal disease with different body reactivity [15].

Today, the issue of the body reactivity influence on wound healing processes in generalized parodontitis remains unstudied. At the same time, we have chosen a specific task to study the features of osteoregeneration after flap surgery without osteoplasty and with the use of osteoplastic material from animals with spontaneous periodontitis with organism normo-, hyper- and hyporeactivity. The different nature (intensity, timing) of osteoregeneration in the alveolar bone, determined through the analysis of morphometric parameters of bone tissue in case of normal and impaired body reactivity, allowed to identify the dependence of wound healing on the initial response to damage. In case of normoreaction, the intensity and timing of the wound process phases were optimal due to providing adequate, uncomplicated wound healing. In case of impaired (hyper- and hypo-) reaction, altered intensity of a cellular phase (increased or decreased) and terms (accelerated or slowed down) resulted in delayed bone wound healing, and as the result, a complicated course was observed. The revealed patterns have proven the necessity to develop methods of the targeted medical correction which would be able to shorten the phases of wound process in case of impaired organism reactivity and make them similar to those that are typical of normoreaction.

Conclusions

1. In case of organism normoreactivity, the following stages of osteoregenation after surgical treatment both without osteoplasty and with the use of osteoplastic material have been revealed: degenerative-inflammatory changes (the 10th day), activation of reparative processes (the 20th day) and active regeneration (the 30th day). The intensity and duration of the wound healing phases provided conditions for normal uncomplicated osteoregeneration of the alveolar bone, which was confirmed by morphometric studies on the correlation between microhemocirculatory bed, connective tissue and bone granulation tissue, bone trabeculae, polymorphonuclear leukocytes, lymphocytes, macrophages, plasma cells.

2. The intensity and duration of the wound healing phases in cases of hyper- and hyporeaction differed from those typical for organism normoreactivity. In case of hyperreaction, the granulocyte-macrophage reaction was more expressed and lasted longer until the 20th day, therefore later, only on the 30th day, there were signs of regeneration. In case of hyporeaction, the granulocyte reaction occurred later (only on the 20th day) and lasted longer, signs of active regeneration were seen later, on the 30th day.

3. Osteoregeneration of alveolar bone in animals with impaired (hyper- and hypo-) organism reactivity was delayed in comparison with that of normoreaction, so it was complicated. The identified patterns occurred regardless of the absence or presence of osteoplastic material in the wound.

4. It is important to choose a targeted drug correction that capable of transforming phases of osteoregeneration after surgical treatment for inflammatory-destructive process in the periodontium with impaired body reactivity into those that are typical for normoreaction, since it provides uncomplicated healing of bone wounds.

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Information about the author:
Yarov Yu. Yu., MD, PhD, Head of the Department of Internship for Doctors-Dentists, Donetsk National Medical University, Kropyvnytskyi, Ukraine.
ORCID ID: 0000-0002-2867-9866

Відомості про автора:
Яров Ю. Ю., д-р філософії, зав. каф. інтернатури лікарів-стоматологів, Донецький національний медичний університет, м. Кропивницький, Україна.

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