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COMPARATIVE DYNAMICS OF INFLAMMATORY MARKERS AND BONE REMODELING IN GUNSHOT WOUNDS AND FRACTURES OF THE UPPER JAW IN THE EXPERIMENT

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Introduction. The nature of gunshot wounds, the development of complications, the course of wound healing with high mortality, and a significant percentage of complications confirm that ammunition with different damaging properties is used in hostilities that contribute to the development of specific changes in the gunshot wound.

The purpose. Gunshot wounds and fractures of the upper jaw were modeled in an experimental study on male laboratory rats for a comparative assessment of the course of the injuries.

Materials and methods. The modelling of injuries was performed following original methods. The intensity of inflammation and the general condition of the body after injury was determined by peripheral blood counts (leukocytes, erythrocytes, and hemoglobin), inflammatory markers (elastase activity and malondialdehyde content), and antioxidant defense in the blood serum, the markers of bone remodeling (alkaline and acid phosphatase activity, elastase, and calcium content) in the jaws with the injured area. The analysis of values was performed on days 7, 14, 21, and 28 after modeling the injuries.

Results. Gunshot wounds of the jaw caused a more pronounced development of general inflammatory reaction than fractures (by 30.3–41.0%), intensification of lipid peroxidation (by 33.3–55.3%), and decrease in the activity of antioxidant defense. Normalization of blood values in rats after jaw fracture was observed on day 14–21, and after gunshot wound – on day 21–28. Resorption of bone tissue in the jaws of rats after gunshot wounds was more intense than after fractures (increasing the activity of elastase – by 17.9–52.8% and acid phosphatase – 29.3–42.9%. Bone formation processes after gunshot injuries began a week later than after fractures. In general, after gunshot wounds of the upper jaw, more significant disorders in the blood and bone tissue were found compared to non-gunshot injuries of the jaw.

Keywords: rats, maxillofacial area, gunshot wounds, fractures, inflammation and bone remodeling values.

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ПОРІВНЯЛЬНА ДИНАМІКА МАРКЕРІВ ЗАПАЛЕННЯ ТА РЕМОДЕЛЮВАННЯ КІСТКОВОЇ ТКАНИНИ У РАЗІ ВОГНЕПАЛЬНИХ ПОРАНЕНЬ ТА ПЕРЕЛОМІВ ВЕРХНЬОЇ ЩЕЛЕПИ В ЕКСПЕРИМЕНТІ
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В експериментальному дослідженні на самцях лабораторних щурів було проведено моделювання вогнепальних уражень та переломів верхньої щелепи для порівняльної оцінки особливостей перебігу пошкоджень. Моделювання травм проводили за оригінальними методиками. Інтенсивність запалення та загального стану організму після пошкодження визначали за показниками маркерів запалення та антиоксидантного захисту у сироватці крові, а також маркерів ремоделювання кісткової тканини у щелепах із пошкодженою ділянкою.

У результаті встановлено, що вогнепальні травми щелепи викликали більш виражений розвиток загальної запальної реакції ніж переломи, інтенсифікації перекисного окиснення ліпідів (на 33–55%) та зниженню активності антиоксидантного захисту (на 13–21%).

Ключові слова: щури, щелепно-лицева ділянка, вогнепальні поранення, переломи, показники запалення та ремоделювання кісткової тканини.

Introduction. The nature of gunshot wounds, the development of complications and the course of the wound healing with high mortality and a great percentage of complications confirm that ammunition with different damaging properties is used in hostilities, which contribute to the development of specific changes in the gunshot wound [1; 2]. Among injuries to different parts of the body gunshot wounds of the maxillofacial area have their own specific features of the wound canal nature, the clinical course of wound healing, and delayed complications [3]. In this regard, many authors point out the need to study the wound process, the values of which are important for assessing the nature of the injury and choosing further surgical management and understanding the gunshot wound formation mechanisms [4–6]. Laboratory modelling of a gunshot wound of the maxillofacial area makes it possible to comprehensively assess the biochemical changes that occur in the facial tissues, which makes it possible to influence the treatment of gunshot wounds of the maxillofacial area in order to improve treatment outcomes and the speed of a patient's recovery.

The aim of the study was to compare the dynamics of some markers of systemic inflammation and bone remodelling in the reproduction of gunshot wounds and fractures of the upper jaw in the laboratory rats.

Materials and methods

The experiments were conducted on 48 white Wistar rats (males, 7 months old, weight 400–450 g), which were divided into the next groups:

– intact (control) group;

– a group with a modelled non-gunshot fracture of the left upper jaw;

– a group with a modelled gunshot wound of the left upper jaw.

The experimental model of gunshot injury in rats was reproduced by using a low-powered 4 mm Flaubert cartridge [7]. The model of non-gunshot fracture of the jaw in rats was reproduced with sharp scissors according to the original method [8].

The duration of the experiment was 28 days. Measurement of values in experimental animals were performed in 4 stages by 5 animals per group: in 7, 14, 21 and 28 days after modelling the injury.

The research with experimental animals was guided by the "Rules for the Treatment of Animals Used in Scientific Experiments..." (Article 26 of the Law of Ukraine "On the Protection of Animals from Cruelty', 2006), and the national "Common Ethical Principles for Animal Experiments" (Ukraine, 2001), which are consistent with Council Directive 2010/63EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

The Bioethics Commission of Odesa National Medical University (Protocol No. 11 of 06.03.2023) confirmed that the study meets the bioethical requirements for experimental work in the biomedical field.

At each stage of the experiment, blood was taken from the tail vein for general analysis, after total bleeding from the heart under thiopental anaesthesia (40 mg/kg), blood was collected to obtain the serum, and the upper jaws with the injured area were isolated, followed by cleaning of muscle tissue. The collected biological material was stored at -20°C before making the biochemical analysis.

The leukocytes, erythrocytes, and haemoglobin count were determined in the capillary blood to reveal the general reaction of the animal body to the injury [9]. The blood serum was used to analyse markers of systemic inflammation (activity of neutrophil elastase, content of malondialdehyde) and a marker of antioxidant defence (catalase activity). In the jaws' homogenates (75 mg/ml of 0.1 M citrate buffer pH 6.1), indicators of bone remodelling were determined: bone formation (alkaline phosphatase activity and content of calcium) and resorption (acid phosphatase and elastase activity) [10].

The statistical processing of the obtained data was carried out using the STATISTICA for Windows XP software and Microsoft Excel 2003 spreadsheets. The correctness of the sample distribution was determined by the Kolmogorov–Smirnov test. Based on the results of the parametric (Student's test) and nonparametric (ANOVA) methods of statistical processing were used. The reliability of the differences in the results was determined if $p<0.05$.

Results of the study and their discussion

The results of the analysis of the effect of injuries on the haematological values шт the experimental rats at different terms after the injury are presented in Table 1.

The table 1 shows that the erythrocytes and haemoglobin count in the blood of the "fracture" group rats did not change significantly as compared to the intact group.

In the "gunshot wound" group, no significant changes were recorded in 7 days of the experiment. However, starting from day 14, according to the nature of the modelled wound, there was a tendency to a certain decrease in erythrocyte count by 14.3% and a significant decrease in haemoglobin by 11.5% ($p<0.05$) compared to the intact animals. On day 21, the erythrocytes count decreased significantly by 13.4% ($p<0.05$) and haemoglobin by 8.2% ($p>0.05$). On day 28 of the experiment, these values were in this group (although $p>0.05$, $p_1>0.05$) (see Table 1).

Leukocytes count in the blood of rats of both experimental groups significantly increased in 7 days after the start of the experiment: in the "non-gunshot fracture" group – 1.7 times ($p<0.002$); in the "gunshot wounds" group – 2.5 times ($p<0.001$) compared to the intact animals. Also, this indicator in the "gunshot wounds" group was significantly higher – 1.5 times ($p_1<0.01$) compared to the "non-gunshot fracture" group. Leukocytosis indicated an active inflammatory response in the body under conditions of modelling pathological conditions, with a predominance in the "gunshot wounds" group (see Table 1).

In 14 days of the experiment, the leukocytes count in the "fracture" group significantly exceeded these values in the intact animals – 1.3 times ($p<0.01$), and on days 21 and 28 this indicator normalised ($p>0.05$) (see Table 1).

In the group with gunshot wounds, the leukocytes count on days 14 and 21 of the experiment was significantly higher – 2.0 times ($p<0.001$) and 1.5 times ($p<0.05$) compared to the intact group. In addition, during the relevant period, this indicator significantly exceeded the value of the group of animals with fracture – 1.5 times ($p_1<0.05$–0.001). In 28 days, the number of leukocytes in the blood of animals after gunshot wounds decreased slightly, but there was a tendency to increasing this indicator by 30.1% ($p>0.05$) compaired to the intact animals and by 26.3% ($p>0.05$) compared to the "non-gunshot fracture" group (see Table 1).

The results of the analysis of the effect of fracture and gunshot wound at different periods of the experiment on the content of malondialdehyde (MDA) and the activity of elastase (markers of inflammation and lipid peroxidation) and the antioxidant enzyme catalase in the blood serum of experimental rats are presented in Table 2.

In the group with uppwe jaw fracture on day 7 of the experiment, the activity of elastase in the blood serum significantly increased – by 67.8% ($p<0.01$), and the content of MDA – by 46.2% ($p<0.05$) compared to the intact group. At the same time, the activity of elastase in the blood of the "gunshot wound" group significantly increased – by 134.7% ($p<0.001$), and the content of MDA – by 136.9% ($p<0.001$) compared to the intact animals, which was 1.4 and 1.6 times higher than in the "fracture" group ($p_1<0.01$). This indicates the presence of systemic inflammation in the body of animals, which is more pronounced after gunshot wounds (see Table 2).

On day 14 of the experiment, the activity of elastase in the "fracture" group significantly exceeded that of the

Table 1

Values of the general blood test in rats at different time periods after a fracture of different origin in the upper jaw

Time period	Groups	Leukocytes, 10^9/L	Erythrocytes, 10^{12}/L	Hemoglobin, g/L
Intact group		10.35±0.54	7.41±0.31	158.65±4.95
7 days	Fracture	17.44±0.95 $p<0.002$	7.84±0.62	162.0±5.96
	Gunshot wound	25.96±1.15 $p<0.001$ $p_1<0.01$	7.90±0.54	151.6±9.24
14 days	Fracture	13.50±0.54 $p<0.01$	7.87±0.54	157.38±7.47
	Gunshot wound	20.33±0.62 $p<0.001$ $p_1<0.001$	6.35±0.30	140.40±3.40 $p<0.05$
21 days	Fracture	10.73±0.66	7.41±0.37	161.24±3.59
	Gunshot wound	15.98±1.64 $p<0.05$ $p_1<0.05$	6.42±0.22 $p<0.05$	145.68±8.39
28 days	Fracture	10.67±0.52	8.15±0.47	153.05±5.24
	Gunshot wound	13.48±1.29	7.05±0.20	165.19±6.34

Note: p – the probability between the values in the "fracture" and "gunshot wound" groups to the intact group; p_1 – the probability between the values in the "fracture" and "gunshot wound" groups.

Table 2

Values of the blood serum in rats at different periods after fracture or gunshot wound in the upper jaw

Time period	Groups	Elastase activity, μkat/L	Catalase activity, mkat/L	Content of MDA mmol/L
Intact group		134.20±9.42	0.195±0.010	0.52±0.04
7 days	Fracture	225.12±14.36 $p<0.01$	0.166±0.011	0.76±0.06 $p<0.05$
	Gunshot wound	314.97±11.45 $p<0.001$ $p_1<0.01$	0.130±0.010 $p<0.01$	1.18±0.06 $p<0.001$ $p_1<0.01$
14 days	Fracture	180.0±13.64 $p<0.05$	0.172±0.012	0.69±0.08
	Gunshot wound	253.73±12.48 $p<0.001$ $p_1<0.02$	0.135±0.013 $p<0.02$	0.92±0.08 $p<0.01$
21 days	Fracture	152.33±11.51	0.170±0.012	0.57±0.05
	Gunshot wound	198.53±11.23 $p<0.02$ $p_1<0.05$	0.147±0.013 $p<0.05$	0.80±0.06 $p<0.02$ $p_1<0.05$
28 days	Fracture	150.45±9.45	0.174±0.015	0.60±0.06
	Gunshot wound	158.86±12.10	0.152±0.010 $p<0.05$	0.54±0.03

Note: p – the probability between the values of the "fracture" and "gunshot wound" groups to the intact group; p_1 – the probability between the values in the "fracture" and "gunshot wound" groups.

intact group – by 34.1% ($p<0.01$) and the content of MDA was by 32.7% higher (although $p>0.05$). In the "gunshot wound" group these values were also significantly higher: elastase activity was by 89.1% higher than in the intact group and by 40.9% than in the "fracture" group ($p<0.001$ and $p_1<0.02$). The content of MDA in the blood serum was by 76.9% higher than in the intact group and by 33.3% than in the "fracture" group ($p<0.01$, $p_1>0.05$) (see Table 2).

At the next stages of the experiment, in 21 and 28 days, the content of MDA in the "fracture" group returned to normal ($p>0.05$). The activity of elastase was by 13.5% and 12.1% higher according to these time periods (although $p>0.05$). In the group of animals with gunshot wounds in 21 days the studied inflammatory markers significantly exceeded the values of intact animals: elastase activity – by 47.9% and the content of MDA – by 53.8% ($p<0.02$). This was significantly higher than in the group of animals with jaw fracture: elastase activity was by 30.3% higher ($p_1<0.05$) and the content of MDA – by 40.4% higher ($p_1<0.05$). In 28 days, there was an excess of elastase activity in the blood serum of animals with gunshot wounds – by 18.4% ($p>0.05$), and the content of MDA reached the values in the intact group (see Table 2).

The activity of catalase, a marker of antioxidant defence, in the blood serum of the group of animals with fracture did not change significantly at all stages ($p>0.05$). In the "gunshot wound" group, in 7 and 14 days of the experiment, a significant decrease in this indicator – by 66.7% and 69.2% ($p<0.01$–0.02) was observed compared with the blood serum of the intact animals. At the next stages, in 21 and 28 days, this value was significantly reduced as compared to the intact group – by 24.6% and 22.1% ($p<0.05$), respectively. A steady decrease in catalase activity in the blood serum of animals with gunshot wounds of the jaw indicates the depletion of the antioxidant defence of the body under conditions of pathology (see Table 2).

Indicators of the state of the bone tissue of the jaws of rats at different time periods after fracture and gunshot wound in the upper jaw are presented in Table 3.

The activity of elastase (a marker of collagen destruction), alkaline and acid phosphatase (markers of bone formation and bone resorption) and calcium content were determined in the bone tissue of the jaws of the experimental rats.

Biochemical analysis of the jaw bone tissue in the "fracture" group in 7 and 14 days after injury revealed a significant increase – 1.8 and 1.5 times in the activity of acid phosphatase (AP) ($p<0.01$–0.02) and elastase – by 42.1% and 28.4% ($p<0.01$–0.05), indicating activation of resorption processes in the bone tissue. At the same time, the activity of alkaline phosphatase (ALP) significantly increased – by 23.6% ($p<0.05$) in 7 days and by 54.5% in 14 days ($p<0.01$). The increase in bone ALP activity indicates active osteogenesis at these follow-up periods. The calcium content in the bone tissue of the jaws at these stages of the experiment decreased by 18.3% and 12.5% compared to the intact group (although $p>0.05$) (see Table 3).

In 21 and 28 days after the fracture, the activity of AP ($p>0.05$) and elastase ($p>0.05$) normalized in the bone tissue of the rat jaws, indicating the end of bone resorption. At the same time, the activity of ALP remained significantly increased – by 37.7% ($p<0.05$) in 21 days, i.e. bone formation processes continued, and in 28 days the activity of ALP corresponded to the intact group level ($p>0.05$). No significant changes of the calcium content in the bone tissue of the rat jaws were observed in 21 and 28 days after the fracture (see Table 3).

Table 3 shows that in the group of animals with gunshot wounds the indicators of bone metabolism were much worse. So, in 7 and 14 days, the activity of AP significantly increased – 2.4 and 2.1 times ($p<0.001$) compared to the intact animals, which was by 29.3% and 42.9% higher than in the bone tissue of the jaws in the "fracture" group

Table 3

Indicators of the state of bone tissue in the jaws of rats at different time periods after a fracture or gunshot wound of the upper jaw

Time period	Groups	AP activity µkat/kg	Elastase activity µkat/kg	ALP activity, µkat/kg	Content of calcium, mmol/g
Intact group		2.59±0.21	18.76±1.32	39.68±2.41	2.73±0.23
7 days	Fracture	4.78±0.34 $p<0.01$	26.66±1.14 $p<0.01$	49.03±2.10 $p<0.05$	2.23±0.20
	Gunshot wound	6.18±0.32 $p<0.001$ $p_1<0.05$	40.75±1.84 $p<0.001$ $p_1<0.002$	41.34±2.15	2.05±0.18
14 days	Fracture	3.87±0.29 $p<0.02$	24.08±1.00 $p<0.05$	61.32±3.45 $p<0.01$	2.39±0.26
	Gunshot wound	5.53±0.24 $p<0.001$ $p_1<0.01$	36.34±1.12 $p<0.001$ $p_1<0.001$	59.96±3.10 $p<0.01$	2.15±0.21
21 days	Fracture	2.83±0.20	21.28±1.10	54.63±4.18 $p<0.05$	2.84±2.84
	Gunshot wound	3.72±0.28 $p<0.05$ $p_1<0.05$	25.09±1.40 $p<0.05$	65.08±3.94 $p<0.01$	2.87±0.20
28 days	Fracture	2.71±0.21	19.42±1.52	43.08±3.26	2.62±0.29
	Gunshot wound	2.88±0.22	19.65±1.42	55.11±3.36 $p<0.02$ $p_1<0.05$	2.97±0.24

Note: p – the probability between the values of the "fracture" and "gunshot wound" groups to the intact group; p_1 – the probability between the values in the "fracture" and "gunshot wound" groups.

($p_1<0.01–0.05$). The activity of bone elastase significantly increased in 7 and 14 days after gunshot wounds – 2.2 and 1.9 times ($p<0.001$), compared to the control group, which was 1.5 times higher than in animals with a jaw fracture ($p_1<0.001$) (see Table 3).

The study demonstrated that against the background of gunshot trauma in animals, there was a tendency to reduction of calcium concentration in the jaws in 7 days by 24.9% ($p>0.05$) and by 21.2% in 14 days ($p>0.05$), respectively, which confirms the intensification of resorption processes in the bone tissue of the rat jaws (see Table 3).

In 21 days after gunshot wound, an increased level of AP activity in the bone tissue of the jaws – by 43.6% ($p<0.05$) was observed, which was higher than in the group after fracture ($p_1<0.05$), and in 28 days this indicator corresponded to the norm ($p>0.05$). Elastase activity in the jaw bone tissue was by 33.7% higher than normal at day 21 ($p<0.05$), and at day 28 it corresponded to normal values ($p>0.05$). The calcium content in the jaws of rats in 21 and 28 days after gunshot wound normalised to the intact group level (see Table 3).

The activity of ALP in the bone tissue of the animals' jaws did not change on day 7 after gunshot injury, in contrast to this value in the "fracture" group ($p_1>0.05$). This indicates an inhibition of the osteogenesis onset after gunshot wounds compared to fracture. The activity of bone ALP increased 1.5 times only on day 14 ($p<0.01$) compared to the intact group. On days 21 and 28 after gunshot wounding, the activity of bone ALP in the jaws of rats remained at a high level: 1.6 times ($p<0.01$) in 21 days and 1.4 times in 28 days (although $p>0.05$) (See Table 3).

The data obtained indicate more pronounced processes of bone resorption in the jaws of rats after gunshot wounds than after fracture. In addition, the processes of osteogenesis after gunshot wounds begin a week later than after fractures.

So, the study revealed more significant disorders in the blood and bone tissue of the jaws in rats after gunshot wounds of the upper jaw compared to non-gunshot injuries.

Conclusions

1. Modelling of jaw fractures in rats on day 7 and 14 caused an increase in leukocytes count in the blood – 1.7 and 1.3 times, respectively. Gunshot injuries of the jaws on days 7, 14 and 21 resulted in a 2.5, 2.0 and 1.5-fold increase in leukocytes count in the blood, respectively. The activity of elastase in the blood serum after fractures increased by 67.8, 47.9 and 34.1% on injury days 7, 14 and 21, respectively, and after gunshot wound at the same period – by 134.7, 89.1 and 53.8%.
2. Reproduction of jaw fractures in rats led to an increase of MDA level in the blood serum by 46.2, 32.7 and 13.5% on injury days 7, 14 and 21, respectively, and gunshot wounds at the same period – by 136.9, 76.9 and 18.4%. Fractures modelling did not affect the activity of catalase in the blood serum of animals, while gunshot wounds caused a decrease in this marker of antioxidant defence by 66.7, 69.2, 24.6 and 22.1% on the 7th, 14th, 21st and 28th day after injury, respectively. In general, blood values in rats after jaw fracture normalized on day 14–21, and after gunshot wound of the upper jaw – on day 21–28.
3. Indicators of jaw bone resorption in rats after fracture were increased only on days 7 and 14: elastase activity – by 42.1 and 28.4%, acid phosphatase – by 84.6% and 49.2%, respectively. Gunshot injuries caused an increase in bone elastase activity by 117.2, 93.7 and 33.7% on days 7, 14 and 21, and acid phosphatase by 138.8, 113.5 and 43.6% on days 7, 14 and 21, respectively. Resorption of the jaw bone tissue after gunshot wounds was more intense and lasted a week longer than after fracture.
4. Jaw fracture caused an increase in alkaline phosphatase activity in the bone tissue by 23.6, 54.5 and 37.7% on days 7, 14 and 21 and a decrease in calcium content by 18.3 and 12.5% on days 7 and 14, respectively. An increase in alkaline phosphatase activity after gunshot injuries was recorded only on day 14 by 51.1%, and on days 21 and 28 – by 64.0 and 38.9%, with a decrease in calcium content by 24.9 and 21.2% on days 7 and 14. Activation of osteogenesis after gunshot wounds began a week later than after fractures, with a more significant decrease in calcium content in the bone tissue of the jaws.

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