ATJ, 2022, №1, 117-124

AZƏRBAYCAN TİBB JURNALI
AZERBAIJAN MEDICAL JOURNAL

DOI: 10.34921/amj.2022.1.019

Ryabenko T.V., Dmitruk S.M., Yarmolenko O.S., Pernakov M.S., Teslıx T.P., Ponırko A.A., Qordienko O.V.

ŞİŞ ƏLEYHİNƏ KİMYƏVİ PREPARATLARIN ZƏDƏLƏNMİŞ BORULU SÜMÜKLƏRİN MEXANİKİ XASSƏLƏRİNƏ TƏSİRİ

Sumı Dövlət Universiteti nəzdində Tibb İnstitutunun Morfologiya kafedrası, Sumı ş., Ukrayna

Məqalədə şiş əleyhinə istifadə edilən kimyəvi preparatların travmatik zədələnməyə məruz qalmış borulu sümüklərin mexaniki xassələrinə təsirini öyrənmək məqsədilə aparılmış tədqiqat işi haqqında məlumat verilmişdir.

Tədqiqat 96 laboratoriya siçovulu üzərində, cinsi xətti nəzərə alınmadan aparılmışdır. Heyvanların bud sümüklərinin orta üçdəbir hissəsində sümük iliyinə qədər nüfuz edən 2 mm diametrli zədələnmə yaradılmışdır. Heyvanlar kontrol (n=24, kimyəvi preparat almayanlar) və eksperimental (n=72, kimyəvi preparat alanlar) olmaqla 2 qrupa bölünmüşdür. Eksperimental qrupun heyvanları da öz növbəsində hər birində 24 baş siçovul olmaqla 3 yarımqrupa ayrılmış, I yarımqrupdakı heyvanların periton boşluğuna 60 mq/m^2 dozada doksorubusin, II yarımqrupun heyvanlarına 600 mq/m^2 5-flüor-urasil, III yarımqrupdakı siçovullara isə 40 mq/m^2 metotreksat yeridilmişdir. Travmadan sonrakı 15-ci, 30-cu, 45-ci və 60-cı günlərdə sümüklərin möhkəmlik həddi və regenerat nahiyəsinin mikrosərtliyi tədqiq edilmişdir.

Tədqiqatdan aydın olmuşdur ki, doksorubisin, 5-flüor-urasil, metotreksat kimi kimyəvi preparatlar travmaya məruz qalmış borulu sümüklərin regeneratının möhkəmliyini və mikrosərtliyini azaldır, eyni zamanda onların böyüməsini də ləngidir. Sümüklərin möhkəmliyinə ən ciddi mənfi təsiri 5-flüor-urasil, sümüyün uzununa və eninə böyüməsinə isə doksorubisin göstərir.

Müəlliflərin fikrincə, kimyəvi preparatların sümüklərinin möhkəmliyini və regenerasiya qabiliyyətini zəiflətməsi bu preparatlarla müalicə alan xəstələrdə sümük sınıqları riskini artıra bilər.

Açar sözlər: *sümük sınıqları, mikrosərtlik, sümüyün möhkəmliyi, şiş əleyhinə mikropreparatlar*

Ключевые слова: *переломы костей, микротвёрдость, прочность, противоопухолевые химиопрепараты*

Keywords: *bone fractures, microhardness, strength, antitumor chemotherapeutics*

Riabenko T.V., Dmytruk S.M., Yarmolenko O.S., Pernakov M.S., Teslyk T.P., Ponyrko A.A., Gordienko O.V.

INFLUENCE OF ANTITUMOR CHEMOTHERAPEUTICS ON MECHANICAL PROPERTIES OF INJURED TUBULAR SKELETAL BONE

Department of Morphology, Medical Institute, Sumy State University, Sumy, Ukraine

The aim of the study was to investigate the effect of antitumor chemotherapeutics on the mechanical properties of the injured long skeletal bone.

The research was carried out on 96 laboratory rats, which were inflicted with a perforated defect with a diameter of 2 mm to the bone marrow canal in the middle third of the femoral shaft. Animals were divided into the control group (n = 24), as well as three experimental (I, II, III, n = 72) ones, which were injected after injurywith theantitumor chemotherapeutics intraperitoneally: I group – with doxorubicin (60 mg/m²), II – with 5-fluorouracil (600 mg/m²), III – with methotrexate (40 mg/m²). Re-administration of appropriate chemotherapeutics was performed in the same doses on each 21st day throughout the experiment. On the 15th, 30th, 45th, and 60th day after injury, the compressive strength limit of the bones and the microhardness of the regenerate were determined.

Anticancer chemotherapy drugs reduce the compressive strength of the bone. On the 60th day after injury, doxorubicin reduces this indicator by 40.08%, 5-fluorouracil – by 40.93%, methotrexate – by 35.19%

compared with the control. Antitumor drugs slow down the growth of bones in width: doxorubicin – by 18.54%, 5-fluorouracil – by 10.24%, methotrexate – by 17.40% compared with the control on the 60th day after injury. Antitumor chemotherapy also reduces the microhardness of the femur in the regenerate area: under the influence of doxorubicin by 37.32% ($p<0.05$), 5-fluorouracil – by 41.47% ($p<0.05$), methotrexate – by 35.83 % ($p<0.05$) in comparison with the control group.

The use of antitumor chemotherapeutics causes a decrease in bone strength and microhardness in the area of bone regeneration, as well as slows bone growth. The most pronounced negative effect on the tensile strength of injured tubular bones has 5-fluorouracil; doxorubicin has the greatest inhibitory effect on bone growth in thickness.

Treatment of fractures is a current problem in medicine. After all, full healing of bone defects helps to restore the anatomical structure of bone and full human life. Bone fractures occur due to the changes in their mechanical properties [1,2]. It is known that the mechanical stability of bone is provided by the impregnation of the collagen matrix with mineral salts, as well as the functioning of non-collagenous proteins [3,4]. The mechanical properties of bone can vary depending on the structural and functional state of bone tissue, age, sex, the presence of local and systemic pathological processes. The most common causes of decreased bone strength are osteoporosis, tumors, dysplastic and dystrophic processes, as well as taking various drugs [5].

To date, an important role is given to the disorders of bone metabolism during the cancer development in the body. They are manifested by hypercalcemia, the development of osteoporosis, metastatic bone lesions, and the occurrence of pathological fractures. Bone fractures in patients with malignant neoplasms can be both independent diseases due to the development of osteoporosis in cancer, and pathological fractures due to the presence of bone metastases [6]. Coleman R. and co-authors investigated that oncocells produce a wide range of cytokines and growth factors when they enter the bone microenvironment. It is a peptide related to parathyroid hormone, prostaglandins and interleukins, which increase the production of receptor activator of nuclear factor kappaB ligand (RANKL).This triggers the process of osteoclasts activation and causes imbalance of bone formation and bone resorption. Bone factors, releasing as the bone matrix is destroyed, enhance the growth and proliferation of cancer cells populations. These multiple interactions between tumor cells and bone environment contribute to further tumor growth and metastasis.As a result, a self-sustaining vicious circle forms between cancer cells and the bone microenvironment [7].

The bone metastases develop when the breast, prostate, lungs, kidneys diseases, and multiple myeloma and often lead to pathological fractures. Given the need for long-term chemotherapy for the treatment of most cancers, reparative bone regeneration in fractures often occurs against the background of the use of anticancer drugs.

The aim of the study was to investigate the effect of antitumor chemotherapeutics on the mechanical properties of the injured long skeletal bone.

Materials and methods. 96 white laboratory male rats 7 months of age weighing 230 ± 10 g were used for the experiment. Rats were in the vivarium of the Medical Institute of Sumy State University on a standard diet and drinking regime with free access to food and water. The study was performed in compliance with the requirements of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes", "General ethical principles of animal experiments" (Kiev).

In a sterile operating room under ketamine anesthesia (50 mg/kg) all animals underwent a perforated defect in the middle third of the femoral diaphysis 2 mm in diameterand depth to the medullary cavity using a spherical dental drill cutter under cooling. Animals were divided into the control (n=24) and three experimental groups (I, II, III, n=72). After injury, the animals of the experimental group were injected intramuscularly with antitumor chemotherapeutics, which are often used in protocols of antitumor chemotherapy. Doxorubicin (60 mg/m²) was injected to the I experimental group of laboratory rats (n = 24), 5-fluorouracil (600 mg/m²) – to the II (n=24), and methotrexate - (40mg/m²) – to the III group of the experimental animals (n=24). Experimental animals were repeated injections of appropriate chemotherapeutics every 21st day through out the experiment.

On the 15th, 30th, 45th, and 60th day after injury, animals of the control and experimental groups were removed from the experiment by decapitation under ketamine anesthesia (100 mg/kg).

The compressive strength limit and microhardness were determinedto evaluate the mechanical properties of bones. The research was performed on a bursting machine R-0.5 with a pendulum force meter and a manual horizontal device. The following indicators were deter-

mined: cross-sectional area (A, mm2), compression load (F, N), compressive strength limit (σ, mPa). Photographs of the injured bones were obtained on an MPB-2 microscope using a 6.0 megapixels SONY digital camera "Cyber-shot".The calipe, digital optical device, and Autodesk-AutocadMechanical software were used to determine the cross-sectional area. The fracture area was determined by computer processing of the photo in a specialized program "ImageProPluS". The compressive strength limit σ, mPa, was calculated by the formula: $\sigma = \frac{F}{A}$, where F is compression load, which causes bone destruction, N; A is initial cross-sectional area of the sample, mm².

We measured the microhardness with a DMH-3 device. We polished the surface of the injured femurs with a diamond suspension and fixed the sample on a metal table by immersion in epoxy resin.After its curing, the hardness numbers were determined at the site of injury and on the surface of the maternal bone at a distance of 10 mm from the site of injury.The Vickers diamond pyramid was pressed into the test specimen under load P (0.1 kg/s). After the action of the load, the imprint in the form of a pyramid with a square base remained on the surface of the sample.The hardness index H, kg/s /mm² was calculated by the formula: $HV = 1.854\left(\frac{F}{d^2}\right)$, where F is load on the pyramid, expressed in N; d is imprint diagonal, mm².

Statistical analysis was performed by computer program MS Excel XP using Student's t-test. The differences at $p<0.05$ were considered significant.

Results.

The mechanical properties of the injured femur of rats change throughout the experiment. Thus, in the control group animals there is a gradual increase in the average compressive strength limit indicator, starting from the 15th day of the experiment. On the 60th day it is 120.24±2.61 mPa, which is 25.85% ($p<0.0001$) more than on the 15th day of the experiment.

In the animals of group I, on the contrary, there is a moderate decrease throughout the experiment. On the 60th day of the experiment, it is 72.04 ± 2.61 mPa, which is 40.08% ($p<0.0001$) less than on the same day in the control group.

In the groupII the compressivestrength limit indicator averages 81.96 ± 3.4 mPa on the 15th day,82.47 ± 3.07 mPa–on the 30th day, 72.06 ± 3.69 mPa –on the 45th day, 71.02 ± 2.94 mPa – on the 60th day.This is 40.93% ($p<0.0001$) less than in the control group.

In the group III, the average value of the compressivestrength limit is 88.36 ± 2.9 mPa on the 15th day, 84.14 ± 1.89 mPa – on the 30th day, 80.53 ± 2.86 mPa – on the 45th day, 77.92 ± 2.72 mPa – on the 60th day. In this group there is a decrease in this indicator by 11.82% ($p<0.0001$) throughout the experiment. Also, on the 60th day it is less then the control by 35.19% ($p<0,0001$).

Thus, the average value of the compressive strength limit in the group II has the largest difference between experimental groups compared with the control (Fig. 1).

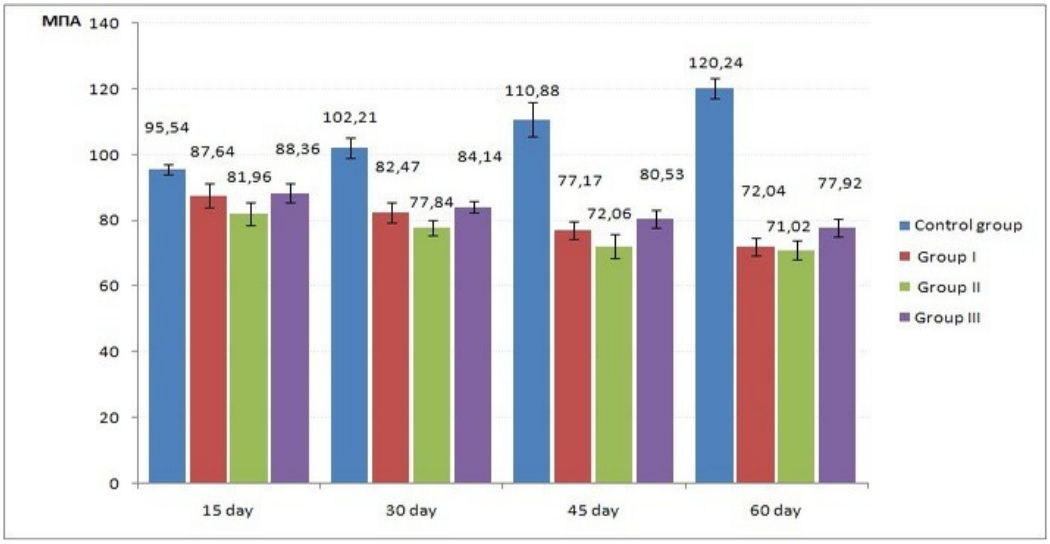

Fig. 1. *Indicators of the rats femur cross-sectional area under the influence of group I, II, III in comparison with the control group ($p<0.05$ when comparing the control group with groups I, II, III on Student's t-test for two independent samples)*

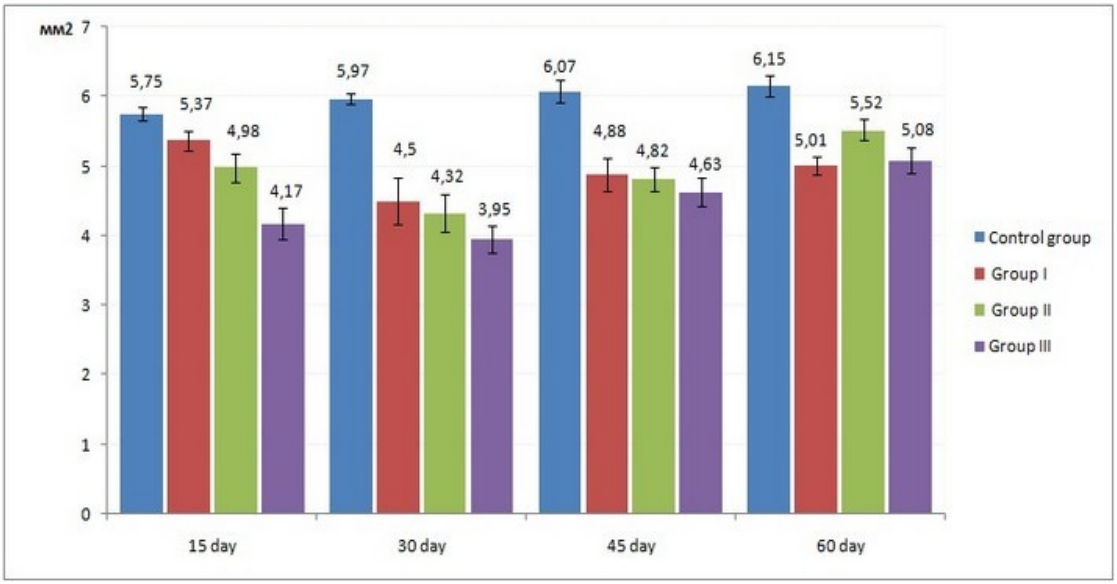

Fig. 2. *Indicators of the rats femur cross-sectional area under the influence of group I, II, III in comparison with the control group ($p<0.05$ when comparing the control group with groups I, II, III on Student's t-test for two independent samples)*

During the experiment, the cross-sectional area of the femur with a defect in the control group increases and equals 6.15 ± 0.15 mm on the 60th day. This is 6.96% ($p = 0.0003$) more than on the 15th day after injury. The increase in the cross-sectional area of the injured femur is due to the physical development of mature animals.In the animals of all experimental groups, there is its gradual decrease on the 30th and 45th day of the experiment and a slight increase on the 60th day, which is associated with the animals growth. Thus, on the 60th day, the average value of the cross-sectional area in the group I is 5.01 ± 0.13 mm, which is 18.54% ($p<0.0001$) less than in the control. In group II, it is equal to 5.52 ± 0.15 mm, which is 10.24% ($p<0.0001$) less than in the control. In group III, the average value of this indicator is 5.08 ± 0.19 mm, which is 17.40% ($p<0.0001$) less than the corresponding indicator of the control group. Thus, the most pronounced changes in the cross-sectional area of the femurs are observed in the group I (Fig.2).

In the control group animals, the microhardness gradually increases throughout the experiment. This indicates the active processes of mineralization in the bone and the improvement of its elastic properties. Thus, on the 60th day of the experiment it is 522.00 ± 17.15 мPa, which is 7.44% more than on the 15th day of the experiment. However, in all experimental groups, the microhardness index gradually decreases.On the 30th day of the experiment, it decreases by 31.62% ($p = 0.0002$) in the animals of group I, by 30.43% ($p<0.0001$) - in the group II, by 26.28% ($p = 0.0005$) - in the group III compared with the control group of animals.On the 45th day there is a further decrease in this indicator by 33.18% ($p<0.0005$) in the group I, by 35.5% ($p<0.0005$) - in the group II, and by 31.43% ($p<0.0005$) - in the group III. On the 60th day after injury, the average value of the microhardness is 327.17 ± 71.53 mPa in the group I and is less than the control by 37.32% ($p<0.0001$). In the group II it is equal to 305.50 ± 38.17 mPa, in the group III - 335.00 ± 41.08 mPa, and is less than the control by 41.47% ($p<0.0001$) and 35.83% ($p<0.0001$), respectively. Therefore, there is a decrease in microhardness in all experimental groups during the experiment. This indicates a slowdown in the formation of a full-fledged callus in the area of injury and a delay in the mineralization of the newly formed bone matrix when using antitumor chemotherapy. The most pronounced decrease in this indicator is observed in the II experimental group (Fig. 3).

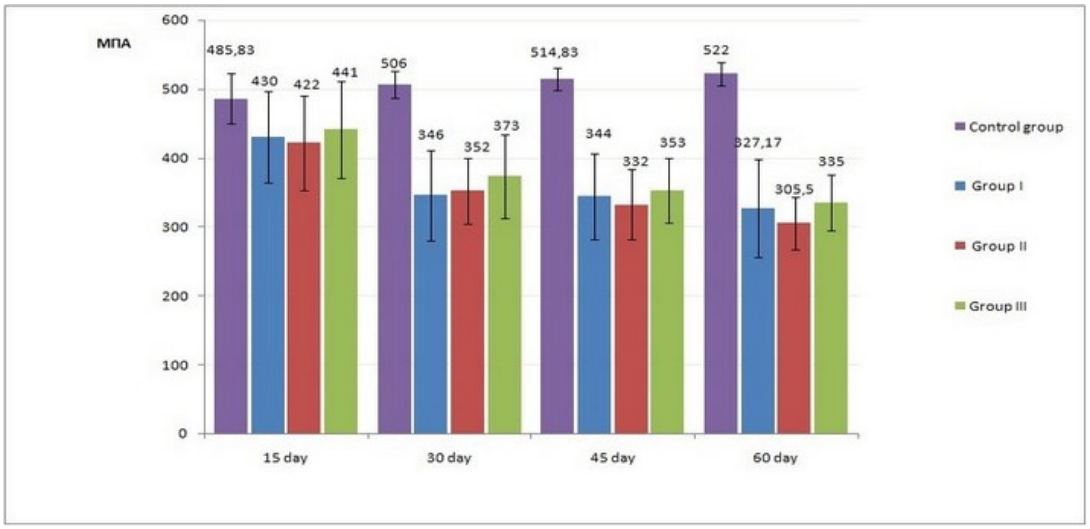

Fig. 3. *Indicators of the rats femur cross-sectional area under the influence of group I, II, III in comparison with the control group ($p<0.05$ when comparing the control group with groups I, II, III on Student's t-test for two independent samples)*

Discussions

Significant progress in oncology in recent decades has led to improved patient survival while raising concerns about the long-term effects of anticancer chemotherapy [8,9]. Side effects in the form of osteopenia and osteoporosis associated with chemotherapy treatment significantly affect the quality of life. Bone health is especially important for patients with breast, prostate, kidney, lungs tumors. According to Hein B.A. there is an accelerated loss of bone tissue is observed in them and it leads to a decrease in bone mineral density, impaired skeletal strength, increased risk of fractures [10]. The results of Sturgeon K.M. indicate that the increased risk of fractures occurs due to low bone mass, changes in bone microarchitecture and increased skeletal fragility [11]. The study of bone tissue bio-mechanical parameters will develop effective methods for the correction of skeletal system disorders and the rapid return of cancer patients to full life.

Our study found an increase in the compressive strength limit of long tubular bones in the control group of animals during the experiment. This is due to the formation of a full bone regenerate in the area of the defect. The rate of remodeling of the femoral defect was fully consistent with the timing of reparative bone regeneration [12]. In the animals of all experimental groups, on the contrary, there was a decrease in the compressive strength with each subsequent term of the experiment.

The negative effects of antitumor chemotherapeutics are confirmed by studies of Handforth C., which found that even a single dose of cytotoxic chemotherapy leads to significant and persistent bone tissue loss due to increased bone resorption [13]. According to Quach J. et al. on day 14 after a single injection of antitumor chemotherapy (5-fluorouracil, cyclophosphamide) there is a increase in bone metabolism under the influence by cytokines such as tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein-1. As a result of their action, osteoclasts are activated. Thus, bone mass loss with antitumor chemotherapy is caused by enhanced osteoclastic bone resorption [14]. In particular, Straszkowski L. et. al. found that doxorubicin treatment induces transforming growth factor-β (TGFβ), which increases osteoclast differentiation and inhibits osteoblast differentiation. This leads to increased bone resorption and accelerated bone tissue loss. In addition, doxorubicin directly affects the production of bone matrix by osteoblasts and reduces the amount of osteoids, slowing down the mineralization of bone regenerate by osteoblasts and causing a decrease in the strength limit [15].

We found a gradual increase in the cross-sectional area of the injured femur in the control group throughout the experiment, due to the physical development of adult rats. In animals

of all experimental groups, on the contrary, there was a decrease on the 30th and 45th day after injury and a slight increase on the 60th day, due to the growth of animals.

Our results are confirmed by Tarasi Rana studies, which found that the use of doxorubicin in children leads to an increased risk of fractures and bone growth retardation in adulthood. Doxorubicin adversely affected the microarchitecture, reducing the volume of trabecular bone and the number of trabecular tissues, increasing the division of the trabeculae themselves. These adverse effects were noticeable both 2 and 10 weeks after itslast dose. This suggests that the effect of doxorubicin on the trabecular bone is long-lasting [16]. Also, the scientific work of Liu Y. et. al. prove the negative effect of methotrexate on bones, manifested by damage to the metaepiphyseal plate of bone growth, a decrease in the thickness of the primary spongiosis and a decrease in the volume of the metaphyseal bone [17].

In our experiment, in all experimental groups, a gradual decrease in the microhardness of the regenerate was observed, indicating a slowdown in the formation of a full-fledged bone callus in the area of damage and a delay in the mineralization of the newly formed bone matrix during the use of antitumor chemotherapy.

Fonseca H. et. al. also emphasize that doxorubicin therapy leads to a decrease in bone strength, which is associated with a significant decrease in the activity of the osteoblasts and osteoclasts mitochondria. This disrupts the processes of bone remodeling, disrupts the trabecular microarchitecture and bone growth. In addition, doxorubicin reduces the normal expansion of periosteal tissue, which plays a crucial role in the ability of the diaphysis to withstand bending and twisting loads. Therefore, doxorubicin has a long-term negative impact on bone resistance to fractures [18].

The inhibitory effect of 5-fluorouracil on the skeletal system described in our experiment is confirmed by Fan C. and Georgiou K.R. They note that the of 5-fluorouracil leds to bone loss upon activation of bone resorption. This is due to an increase in the number of osteoclasts in the metaphase, contributing to a decrease in trabecular bone volume. These changes lead to a decrease in bone microhardness and contribute to fractures in patients during antitumor chemotherapy [19].

The negative effect of methotrexate on the mechanical properties of bones found in our study is confirmed by Fan C.M. The researcher notes that long-term treatment with high doses of methotrexate inhibits the proliferation of osteoblasts and preosteoblasts, causes a decrease in their density. This leads to increased bone loss and reduced bone microhardness. In particular, with short-term use of methotrexate, bone trabeculae were smaller in number and more divided, which is consistent with the results of a short-term study in rats [20]. Studies by Shandala T. have shown that methotrexate treatment increases osteoclasts by 1.8 times due to increased expression of inflammatory cytokines IL-6 (10-fold) and IL-11 (2-fold). These changes led to the activation of osteoclastogenesis with subsequent loss of about 35% of the trabecular bone and a decrease in bone microhardness [21].

Conclusions

The use of antitumor chemotherapeutics (doxorubicin, 5-fluorouracil, methotrexate) in the experiment slows down the growth of injured tubular bones in width and causes changes in their mechanical properties, which is manifested by a decrease in compressive strength limit and reduced microhardness of bone tissue and is regarded as a risk factor for fractures in patients undergoing anticancer chemotherapy. Among antitumor drugs, 5-fluorouracil has the most pronounced negative impact on the strength limit of injured tubular bones; doxorubicin has the most inhibitory effect on bone growth in thickness.

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Рябенко Т.В., Дмитрук С.Н., Ярмоленко О.С., Пернаков Н.С., Теслык Т.П., Понырко А.А., Гордиенко Е.В.

ВЛИЯНИЕ ПРОТИВООПУХОЛЕВЫХ ХИМИОПРЕПАРАТОВ НА МЕХАНИЧЕСКИЕ СВОЙСТВА ТРАВМИРОВАННОЙ ТРУБЧАТОЙ КОСТИ СКЕЛЕТА

Кафедра морфологии, Медицинский институт,
Сумский государственный университет, Сумы, Украина

Резюме. **Цель работы** – изучить влияние противоопухолевых химиопрепаратов на механические свойства травмированной длинной кости скелета.

Исследования выполнили на 96 лабораторных крысах, которым наносился дырчастый дефект

диаметром 2мм до костномозгового канала в области средней трети диафиза бедренной кости. Животные были разделены на контрольную (n=24) и три экспериментальные (I, II, III, n=72) группы, которым после нанесения травмы и через каждый последующий 21-й день эксперимента вводили внутрибрюшинно соответствующие противоопухолевые химиопрепараты: I – доксорубицин (60 мг/м), II – 5 фторурацил (600 мг/м), III – метотрексат (40 мг/м). На 15-е, 30-е, 45-е, 60-е сутки после травмы определяли предел прочности костей на сжатие и микротвёрдость регенерата.

Исследование показало, что противоопухолевые химиопрепараты уменьшают прочность кости на сжатие. На 60-е сутки после травмы доксорубицин снижает данный показатель на 40,08%, 5-фторурацил – на 40,93%, метотрексат – на 35,19% по сравнению с контролем. Противоопухолевые химиопрепараты замедляют рост костей в ширину: доксорубицин – на 18,54%, 5-фторурацил – на 10,24%, метотрексат – на 17,40% по сравнению с контролем на 60-е сутки после травмы. Химиотерапия приводит к уменьшению микротвёрдости кости в области регенерата. При введении доксорубицина на 60-й день эксперимента показатель микротвёрдости ниже на 37,32%, чем в контрольной группе, 5-фторурацила – на 41,47%, метотрексата – на 35,83%.

Таким образом, применение противоопухолевых химиопрепаратов вызывает снижение предела прочности костей и микротвёрдости в области костного регенерата, а также замедляет рост костей. Наиболее выраженное отрицательное влияние на прочность травмированных трубчатых костей оказывает 5-фторурацил, на рост кости в толщину – доксорубицин.

Author for correspondence:

Tatiana Riabenko – Assistant of the Department of Morphology, Sumy State University, Sumy, Ukraine.

ORCID: 0000-0003-2740-389X

Автор для переписки:

Татьяна Рябенко – Ассистент кафедры морфологии Сумского государственного университета, г. Сумы, Украина.

ORCID: 0000-0003-2740-389X