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Changes in the blood indicators of experimental animals by introduction of the components based on lanthanide ions and calcium into the zone of a femoral fracture

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Introduction Reduction of time to restore bone integrity remains one of the main problems in traumatology and orthopedics. To solve this problem, various kinds of components have been used, one of which are bisphosphonates. This article presents an experiment, the purpose of which was to study the effect of components based on etidronates of lanthanide or calcium on blood indicators by different ways of their introduction into the femoral fracture site in experimental animals. **Materials and methods** Studies were conducted on 75 male rats aged 5–6 months, weighing 300–350 g. A femoral fracture was modeled in all animals, and retrograde intramedullary osteosynthesis was performed. Animals were divided into 5 groups. Group 1 received no components; a component based on etidronates of lanthanide and calcium was introduced in group 2 through a catheter; group 3 had paraossal administration of etidronates of lanthanide and calcium; group 4 had paraossal introduction of a component based on etidronate calcium through a catheter; and group 5 had introduction of components based on etidronates and calcium. Animals received the investigated components twice in the fracture zone on days 3 and 5 after the operation, except the comparison group. **Results** In groups with a catheter, the most pronounced local inflammatory response was observed. Changes in hemoglobin concentration were observed in all groups, in the early (7 days) period. It was found that in rats which were injected with components containing lanthanides, the average content of hemoglobin, erythrocytes and leukocytes were identical to those of group 1. **Conclusion** The study revealed that the components, which include lanthanide ions do not cause negative changes in the rat blood according to hematological tests.

Keywords: rat, femoral bone, hematological values

One of the important areas of traumatology is restoration and repair of damaged bone tissue [1, 2]. In addition to improving osteosynthesis, medicinal compounds that stimulate reparative processes have been searched currently. Bone regeneration may be stimulated by components that have osteoinductive and osteoconductive properties, do not cause toxic and allergic reactions of the body [3]. Nowadays, various types of drugs aimed at stimulating osteogenesis have been known, such as "Osteogenon" [4, 5, 6]. It consists of hydroxyapatite and ossein and has been widely used for osteoporosis [7]. Another drug, "Valpan", based on hydroxyapatite and collagen, has been applied to accelerate osteogenesis [8]. Some authors have studied the injection of the biocomposite "LitAr" and established its positive effect in delayed osteoreparation [9].

Preparations that include bisphosphonates have also found a widespread use. Their action is aimed

at decrease of resorption [10]. In addition, their use also normalizes the mineralization processes to increase bone mass and strength [11]. However, bisphosphonates in a state of a solution cannot be concentrated for a long time in the zone of local administration, and it remains a problematic issue in the treatment with their use[12]. Therefore, lanthanide ions have been used. These are effective catalysts of hydrolytic sciccion of phosphate-ether bonds, including strong bonds in DNA [13].

The literature on this topic provides little information about the body's response to the use of lanthanides. Therefore, the objective of our study was to study the effect of the agents based on the ethidronates of lanthanide ions and calcium on hematological parameters in different modes of their delivery to the fracture zone of the femur in experimental animals.

MATERIAL AND METHODS

The studies were carried out in accordance with GOST ISO 10993 (R) and approved by the local ethics committee at the Federal State Budgetary Educational Institution of Higher Education *Kazan State Medical University* of the Ministry of Health of Russia (protocol No. 10 dated December 18, 2018) [14].

Experimental animals were 75 male rats. The age of the rats was 5–6 months, weight 330–360 g. The animals formed 5 groups, 15 rats each.

An osteotomy was performed [15] in all the animals followed by retrograde nailing into the medullary canal [16]. Implants made of medical steel 12X18H9 had a diameter of 0.8 mm and 1 mm with feather-like sharpening.

Group 1 did not receive any componentio Components based on etidronates of lanthanide and calcium were introduced in group 2 through a catheter; group 3 had paraossal administration of components based on

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etidronates lanthanide and calcium by injections into the fracture zone from the lateral and medial sides [17, 18]; group 4 had paraossal introduction of a component based on calcium etidronate and (without lanthanide etidronate) through a catheter; and group 5 had paraosseous injections of the components based on calcium etidronate (without lanthanide) into the fracture zone from the lateral and medial sides. All components were introduced into the fracture zone on the 3rd and 5th day after the operation [19] at a dose of 0.2 ml on each side (medially and laterally) paraossally or 0.4 ml through the catheter.

Two groups of animals (2 and 4) had a pre-installed catheter in the fracture zone. To install the catheter, a hole of a diameter of 1.5 mm was drilled above the osteotomy zone as planned and a catheter was inserted into the hole, leading it to the medullary canal. The catheter cannula remained under the skin. An intradermal suture was applied.

During the entire experimental period, animals were monitored clinically for 30 days. Their general condition, nutritional excitability, motor activity, body temperature and local body reactions were observed.

Blood was collected to determine hematological parameters from the tail vein (v. Coccygea) in a volume of 1 ml before surgery, on the 7th, 14th and 30th day after surgery. To obtain reliable data, a new group of animals was taken for each term.

Erythrocyte sedimentation rate (using the Panchenkov apparatus and pipettes), hemoglobin concentration (hemometer and Sali pipettes), number of red blood cells (counts in the Goryaev chamber) and leukocytes (counts in the Goryaev chamber) were determined; morphological composition of leukocytes was determined according to the generally accepted method [20]. Axioscop-Zeiss AG microscope was used.

Statistical processing methods Digital data were processed using the SPSS 13.0 software. Using the Kolmogorov-Smirnov criterion, the normality of the distribution of indicators was evaluated. Student's test was used for pairwise comparisons. Analysis of variance was used for comparing three or more groups. Subsequent intergroup comparisons were performed using Student's test with Bonferroni correction. Significant differences were considered at p < 0.05 [16].

RESULTS

During the clinical study, no significant changes in the general condition of experimental rats were detected. The restoration of food excitability was observed after 6 hours, and motor activity an hour after surgery. The body temperature throughout the entire period remained within the physiological norm and was on average 7 °C on day 7 (Table 1). However, in group 4 with the introduction of components based on calcium ethidronate (without lanthanides) through the catheter, changes were observed on the 30th day of the experiment; this parameter increased by 2 % (p = 0.001).

There was an inflammatory reaction at the site of the postoperative wound, more pronounced in groups 2 with the introduction ethidronates of lanthanide and calcium through a catheter and 4 with the introduction of calcium ethidronate (without lanthanides) through a catheter. The reaction was manifested by edema, increased local temperature and exudation. All animals had moderate supporting limpness.

The analysis of blood morphological parameters revealed changes in the dynamics of the erythrocyte

sedimentation rate (ESR) on the 7th day. In group 3, this indicator increased significantly by 1.8 times (p = 0.016), and in group 5 without lanthanide ions, significant differences were observed, as this indicator increased by 1.6 times (p = 0.016) (Table 2). In other groups, no significant changes were observed.

In group 4 with the introduction of calcium ethidronate (without lanthanide) using a catheter, ESR significantly decreased on the 14^{th} day by 2.6 times (p = 0.007) relative to group 1 without the components. On day 30, it was found that this indicator in group 2 with the introduction of the components based on ethidronates of lanthanide and calcium through a catheter and group 3 with the paraossal administration of the components based on the ethidronates of lanthanide and calcium significantly increased by 1.8 times relative to group 1 without administration of the components (p = 0.019) and group 5 with a paraosseous administration of the components based on calcium ethidronate (without lanthanide) (p = 0.019).

Temperature measurements in the postoperative period (°C)

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Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	37.3 ± 0.10	37.0 ± 0.03	37.0 ± 0.02	37.1 ± 0.05	37.2 ± 0.12	37.1 ± 0.05
Group 2	37.1 ± 0.09	37.1 ± 0.04	37.1 ± 0.05	37.2 ± 0.10	37.1 ± 0.05	37.0 ± 0.04
Group 3	37.1 ± 0.09	37.0 ± 0.03	37.0 ± 0.04	37.2 ± 0.06	37.2 ± 0.08	37.2 ± 0.11
Group 4	37.1 ± 0.13	37.0 ± 0.03	37.2 ± 0.08	37.1 ± 0.03	37.2 ± 0.09	37.8 ± 0.11*
Group 5	37.2 ± 0.05	37.1 ± 0.05	37.2 ± 0.11	37.1 ± 0.03	37.0 ± 0.04	37.2 ± 0.15

Notes: * – statistically significant differences with preoperative values at p < 0.05

Table 1

Table 2 Change in the erythrocyte sedimentation rate in the blood of animals at the stages of the study (mm/h)

Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	0.6 ± 0.1	0.5 ± 0.00	0.5 ± 0.00	0.8 ± 0.12	0.5 ± 0.00	0.5 ± 0.00
Group 2	0.8 ± 0.2	0.5 ± 0.12	0.8 ± 0.12	0.6 ± 0.10	0.7 ± 0.20	0.9 ± 0.10#**
Group 3	0.3 ± 0.00	0.4 ± 0.13	0.5 ± 0.00	0.5 ± 0.00	0.5 ± 0.00	0.9 ± 0.10*#**
Group 4	0.9 ± 0.1	0.7 ± 0.12	0.7 ± 0.12	0.3 ± 0.04 #	1 ± 0.00	0.6 ± 0.12
Group 5	0.3 ± 0.04	0.5 ± 0.00 *	0.4 ± 0.04	0.5 ± 0.00	0.6 ± 0.10	0.5 ± 0.00

Notes: * – significantly significant differences with preoperative values at p < 0.05; ** – significantly significant differences with group No. 5 at p < 0.05; # – significantly significant differences with group No. 1 at p < 0.05

A significant decrease in the concentration of hemoglobin (Hg) was found on the 7^{th} (p = 0.001) and on the 30th days of the experiment (p = 0.007) in group 1 rats without the introduction of components relative to the preoperative parameters. However, it should be noted that these values remained within the physiological norm. In group 2, a decrease in Hg by 1.27 times (p = 0.005) on day 7 and by 1.25 times (p = 0.002) on day 14 was observed. In group 3 with the paraossal administration of the component based on ethidronates of lanthanide and calcium and in group 4 with the introduction of the components based on calcium ethidronate (without lanthanide ions) through the catheter on day 7, there was a similar decrease by 1.23 times (p = 0,0001, group 3; p = 0.028, group 4) (Table 3).

Leukopenia (a twofold decrease in this indicator, p = 0.027) was recorded in the experimental animals with respect to the initial indicator in group 4 on day 14.

In group 5 with the paraossal administration of calcium ethidronate (without lanthanide), a decrease (Table 4) in the number of leukocytes by 2.1 times (p = 0.031) was recorded on day 30 (p. 4). Group 1 without the introduction of any component and group 3 with the paraossal administration of ethidronates of lanthanide and calcium underwent the smallest fluctuations within the physiological norm.

The number of erythrocytes (Er) significantly decreased on day 7 in group 1 (p = 0.017) and in group 2 with the introduction of the components based on the ethidronates of lanthanide and calcium through a catheter (p = 0.011). In group 4 of calcium ethidronate (without lanthanide) introduction through a catheter on day 14, this indicator decreased by 1.3 times (p = 0.015) (Table 5). However, these indicators were within the physiological norm, also in the other groups.

Table 3 Change in the concentration of hemoglobin in the blood of animals (g/l)

Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	188 ± 7	150 ± 6*	207 ± 10	185 ± 6	202 ± 5	170 ± 4*
Group 2	184 ± 6	144 ± 3*	212 ± 7	169 ± 10*	175 ± 12	178 ± 5
Group 3	186 ± 2	151 ± 1*	210 ± 10	198 ± 7	179 ± 6	180 ± 8
Group 4	212 ± 14	171 ± 11*	198 ± 8	164 ± 14	178 ± 6	175 ± 6
Group 5	171 ± 11	170 ± 27	182 ± 4	183 ± 7	167 ± 17	193 ± 13

Notes: * – statistically significant differences with preoperative values at p < 0.05

Table 4 Change in the content of leukocytes in the blood of animals (10⁹/l)

Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	9.2 ± 2.0	8.1 ± 1.2	11.9 ± 1.6	10.1 ± 1.1	9.2 ± 1.6	8.3 ± 1.4
Group 2	10.1 ± 0.9	6.8 ± 1.2	10.5 ± 1.4	6.3 ± 1.3	14.8 ± 2.0	10.1 ± 2.1
Group 3	12.9 ± 2.1	10.9 ± 0.6	12.7 ± 2.4	10.5 ± 0.7	13.0 ± 2.3	11.7 ± 3.0
Group 4	12.6 ± 3.4	8.5 ± 1.2	16.4 ± 2.6	8.2 ± 1.6 *	13.2 ± 2.2	11.0 ± 2.7
Group 5	10.3 ± 2.1	7.3 ± 1.8	17.2 ± 1.9	10.1 ± 1.6	15.1 ± 2.8	7.1 ± 1.4*

Notes: * – statistically significant differences with preoperative values at p < 0.05

Table 5 Change in the content of erythrocytes in the blood of animals $(10^{12}/1)$

Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	6.1 ± 0.1	$4.7 \pm 0.2*$	6.1 ± 0.3	5.8 ± 0.3	6.3 ± 0.4	5.9 ± 0.1
Group 2	6.4 ± 0.3	4.5 ± 0.3 *	5.7 ± 0.4	5.5 ± 0.3	5.9 ± 0.2	6.0 ± 0.2
Group 3	5.8 ± 0.2	4.8 ± 0.5	7.0 ± 0.2	6.4 ± 0.4	6.6 ± 0.3	6.1 ± 0.2
Group 4	6.5 ± 0.3	5.9 ± 0.4	6.8 ± 0.5	5.2 ± 0.6 *	5.5 ± 0.4	5.6 ± 0.2
Group 5	5.8 ± 0.3	5.1 ± 0.2	6.0 ± 0.3	7.0 ± 0.1	5.2 ± 0.3	6.4 ± 0.3

Notes: * - statistically significant differences with preoperative values at p < 0.05

On the 7th day of the experiment, a decrease in the lymphocyte content in group 2 with the introduction of components based on the ethidronates of lanthanide ions and calcium through the catheter by 20 % (p = 0.004) and in group 3 with the paraossal administration of components based on the ethidronates of lanthanide and calcium by 27 % (p = 0.012) with respect to the preoperative values was revealed. Whereas on day 30 in group 1 without the introduction of the components, this indicator decreased by 22 % (p = 0.037). On the 14^{th} day, lymphocytopenia was observed in group 2 with the introduction of the components based on the ethidronates of lanthanide ions and calcium through a catheter and had a significant difference of 23 % from group 5 with the paraossal administration of the components without lanthanide ions (p = 0.024) and from group 3 with the paraossal administration of the components containing lanthanide ions (p = 0.046), (Table 6). In group 4 with the introduction of the components without lanthanide ions through a catheter, a slight decrease in lymphocytes was observed over the entire period. In group 5 with the paraossal administration of the components based on calcium ethidronate (without lanthanide ions), the lymphocyte content remained almost unchanged throughout the experiment. A significant increase by 71 % (p = 0.041) in segmented neutrophils on day 30 in group 1 without the introduction of the components was revealed with respect to preoperative values. This indicator increased on days 7 and 14 in group 2 with the introduction of lanthanide ion component through the catheter by 56 % (p = 0.001) and 38 % (p = 0.042), respectively.

On the 7^{th} day, the number of segmented neutrophils in group 3 with the paraossal administration of the components containing lanthanide ions increased by 66 % (p = 0.005) and on the 30th day by 50 % (p = 0.030) (Table 7). The nature of changes in this indicator in other groups did not have significant differences.

In group 5 with the paraossal administration of calcium ethidronate (without lanthanide ions) on day 7, a significant decrease by 62% (p = 0.044) was observed relative to group 3 with the paraossal administration of components based on the ethidronates of lanthanide ions and calcium.

On the 7^{th} day, the number of stab neutrophils in group 5 with paraossal administration of the components based on calcium ethidronate (without lanthanide ions) was increased by 3.7 times (p = 0.048) relative to the initial values. On the 14th day in group 4 with the introduction of the components based on calcium ethidronate (without lanthanide ions) through a catheter, a 2.4-fold decrease in this indicator was observed (p = 0.025). On day 14, a significant increase in the index in group 2 with the introduction of the components based on the ethidronates of lanthanide and calcium through a catheter was revealed by 75–95 % (p = 0.001) relative to other groups (Table 8).

Table 6

Dynamics of the lymphocytes content in the blood of animals (%)

Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	80.2 ± 5.0	83.6 ± 4.6	84.0 ± 4.6	84.0 ± 5.5	88.6 ± 1.5	69.2 ± 6.4*
Group 2	81.6 ± 2.6	65.0 ± 0.5*	76.8 ± 3.1	67.4 ± 3.2#	73.0 ± 18.3	86.6 ± 3.9
Group 3	83.2 ± 1.5	60.4 ± 5.7*	85.6 ± 2.3	85.2 ± 1.9	85.2 ± 0.9	75.2 ± 3.8
Group 4	83.8 ± 3.6	70.2 ± 8.8	86.4 ± 2.5	83.6 ± 4.5	76.7 ± 6.2	68.7 ± 7.4
Group 5	87.2 ± 1.6	82.0 ± 4.3	84.4 ± 1.2	87.0 ± 3.7	72.6 ± 7.3	75.6 ± 5.2

Notes: * – significantly significant differences with preoperative values at p < 0.05; # – significantly significant differences between the values of group 2 and groups 3 and 5, p < 0.05

Table 7

Dynamics of the content of segmented neutrophilic granulocytes in the blood of animals (%)

Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	16.8 ± 4.5	14.6 ± 4.4	13.6 ± 3.9	14.6 ± 5.1	8.0 ± 1.0	27.4 ± 6.7*
Group 2	14.2 ± 1.8	32.6 ± 0.8*	15.8 ± 2.1	25.4 ± 3.0*	23.4 ± 16.7	11.2 ± 3.5
Group 3	12.2 ± 1.5	35.6 ± 5.4*	10.4 ± 2.7	12.8 ± 2.4	10.2 ± 0.8	20.2 ± 3.5*
Group 4	14.6 ± 2.8	24.6 ± 7.5	10.8 ± 2.4	12.6 ± 3.3	18.7 ± 5.3	25.0 ± 6.4
Group 5	10.6 ± 1.3	13.4 ± 3.5#	12.6 ± 0.5	9.6 ± 2.9	21.6 ± 6.0	20.6 ± 4.7

Notes: * – significantly significant differences with preoperative values at p < 0.05; # – significantly significant differences between the values of group 5 and group 3, p < 0.05

 $Table\ 8$ The dynamics of the content of stab neutrophilic granulocytes in the blood of animals at the stages of the study (%)

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Group /Term	Before operation	7 days	Before operation	14 days	Before operation	30 days
Group 1	2.2 ± 1.4	1.2 ± 0.3	2.2 ± 0.6	0.6 ± 0.2	2.4 ± 1.0	2.8 ± 0.5
Group 2	3.0 ± 0.9	1.2 ± 0.3	5.0 ± 2.1	7.0 ± 0.7 #	2.6 ± 1.8	1.8 ± 0.6
Group 3	3.2 ± 0.5	1.6 ± 0.6	1.6 ± 0.6	1.6 ± 0.9	2.8 ± 1.1	3.6 ± 1.2
Group 4	1.2 ± 0.9	3.0 ± 0.7	2.4 ± 0.5	1.0 ± 0.3 *	4.2 ± 1.1	5.2 ± 1.1
Group 5	0.8 ± 0.3	3.0 ± 1.0*	1.4 ± 0.6	1.2 ± 0.5	4.6 ± 1.6	1.6 ± 0.6

Notes: * – significantly significant differences with preoperative values at p < 0.05; # – significantly significant differences between the values of group 2 and other groups, p < 0.05.

Throughout the experiment, the monocyte count underwent insignificant changes in the animals and remained within the norm.

On the 14th day, eosinopenia was established compared with preoperative data only in group 2 with

the introduction of the components based on of the ethidronates of lanthanide and calcium ions through a catheter (p = 0.034). In animals of all groups throughout the experiment, basophils were absent in the blood.

DISCUSSION

It is well known that any organism reacts with any foreign body invading it, as a result of which the decay products "poison" it, causing inflammation and tissue rejection [21]. As our studies have shown, the method of introducing components through a catheter is ineffective. The groups of animals with introduction of the components had the most pronounced exudative process and an increased body temperature, which is the result of a foreign body (catheter) under the skin. Also, in these groups, changes in blood indices were more pronounced, and therefore, a correlation was observed in animals of these groups while analyzing clinical and hematological changes.

Features of the body's response to many pathological conditions are such that changes in the blood occur long before the first symptoms appear.

In the course of the study, it was found that the introduced components based on the ethidronates of lanthanide and calcium ions, intended to activate bone repair, lead to an increase in the erythrocyte sedimentation rate relative to preoperative values by 30 days. However, according to the literature data, it was found that this indicator can normally reach up to 1.5 mm / hour, whereas in our studies it was equal to 0.9 ± 0.10 mm / hour, which is not a deviation [22]. Also, in these groups, at different observation periods, an increase in segmented neutrophils and a decrease in lymphocytes at the early (7 days) observation periods were noted, which may be associated with the body's response to trauma. By the end of the experiment (30 days), similar changes were observed in the group without components; however, they did not pass beyond the physiological norm. According to a number of studies, the boundary of the volatility of segmented neutrophils can reach 35 % [23], and of the lymphocyte content 55-98 % [23, 24].

Currently, there is some information about the effect of lanthanides on peripheral blood parameters [25]. Our analysis of hematological parameters revealed a slight decrease in the hemoglobin concentration in the early stages in all groups, as well as in the group with the paraossal administration of the components based on ethidronates of lanthanide and calcium, the indicators of which did not exceed the physiological norm. A group of authors conducted an experiment in which the effect of a contrast medium containing a lanthanide (gadolinium) was investigated. He showed that lanthanide did not cause significant changes in hemoglobin levels [26].

Analyzing the findings obtained by us it was found that the changes that occurred in the group during the paraossal administration of components containing lanthanide ions and in the group without the introduction of components changed identically. It was determined that the average content of erythrocytes and leukocytes in the experimental rats did not differ from those in animals of the group where the components were not administered.

For comparison, other authors conducted hematological studies on rabbits to study the effect of components containing lanthanides by their local introduction into the perforation defect. The studies found that the changes in the quantitative indicators of leukocytes and erythrocytes occurred mainly in the early stages, which may indicate the acute phase of the inflammatory process; however, these changes were similar both in the group without the introduction of components and in the group with the introduction of these components [27].

Summarizing the results of the study, we conclude that the observed changes in the group with the paraossal administration of the components containing lanthanide ions were insignificant, and returned to physiological values by the end of the experiment. In similar studies in rabbits, similar results were observed by double local introduction of lanthanides into the perforation defect, with no pathological changes in blood parameters [14].

CONCLUSIONS

Due to the fact that the changes in blood parameters in the experimental groups remained within the reference values and were similar to the values in group 1, where the components were not introduced, it can be assumed that the revealed changes are characteristic of the body's response to surgery.

It was found that the content of eosinophils was within the physiological norm. It confirms the absence

of an allergic reaction to the components and their doses.

The experimental results reflect the functional state of the animal organism by the introduction of the components based on ethidronates of lanthanide and calcium ions, as well as with the introduction of components based on calcium ethidronate (without lanthanides) into the fracture zone and are quite comparable with the findings of the previous studies [20, 27, 28].

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