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Laboratory criteria for pathological process monitoring in patients with chronic osteomyelitis of the lower leg at the stages of restorative treatment

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Purpose Search for laboratory criteria of pathological process monitoring in patients with chronic osteomyelitis of the tibia at the stages of its management using the method of transosseous distraction osteosynthesis. **Materials and methods** Biochemical parameters of blood serum were studied in 15 patients with chronic posttraumatic osteomyelitis of the tibia. Sequester necrectomy with subsequent osteosynthesis of the tibia with the Ilizarov apparatus was performed in all patients at the first stage. At the second stage, the defect was filled in with distraction regenerate according to Ilizarov. Depending on the bone defect size, the patients were divided into two groups. The defect size was from 3 to 5 cm in patients of the first group (n = 7, mean age 42.4 ± 6.9 years). In the patients of the second group (n = 8, mean age 37.5 ± 7.8 years) the size of the defect was from 7 to 12 cm. **Results** It was found that the changes in the activity of the bone isoenzyme of acid phosphatase (TRAP), alkaline phosphatase, creatine phosphokinase, lactate and C-reactive protein (CRP) did not differ significantly between the groups during their treatment. At the same time, the concentration of CRP, sialic acids and the activity of TRAP in the first stage perids of treatment was significantly increased in patients of both groups relative to the reference norm. In patients of the second group, the concentration of sialic acids was higher than the values of group 1 and the reference group in the periods of 7-21 days of fixation. Nevertheless, at the beginning of the second stage of treatment (distraction), the level of all the studied parameters was not significantly different from the norm. **Conclusion N**ormalization of TRAP activity, concentration of CRP and sialic acids values can be attributed to additional diagnostic features on the basis of which it is possible to start the second stage of treatment (distraction) in patients with chronic osteomyelitis of the tibia.

Keywords: tibia, chronic osteomyelitis, transosseous distraction osteosynthesis, blood, biochemistry

INTRODUCTION

The need to monitor the suppression of the inflammatory processes along with a parallel evaluation of reparative bone regeneration in order to assess the effectiveness of treatment in chronic osteomyelitis is an urgent task.

It was shown that laboratory methods are the most accessible methods of diagnosing purulent bone complications, including osteomyelitis, as they are most standardized and able to provide the diagnosis when clinical manifestations are absent [1–5].

Most of the tests developed for the diagnosis of osteomyelitis are indicators of the immunological status. They are also used for monitoring osteomyelitis eradication [6–8].

However, the search for indicators for laboratory monitoring of the degree of osteomyelitis focus debridement with simultaneous assessment of bone repair has not found sufficiently sensitive tests yet [9–12].

The task of designing a laboratory monitoring protocol is exacerbated by the fact that there are many factors that significantly increase the variability and reduce the sensitivity and specificity of laboratory tests (stage and duration of treatment, concomitant therapy, associated diseases, etc.). In this regard, the issue of finding additional objective and sensitive criteria for assessing the effectiveness of inflammatory processes suppression in patients with purulent musculoskeletal system lesions during various periods of restorative treatment remains a problem that is little solved.

The aim of the study was to identify laboratory criteria for monitoring the pathological process in patients with chronic osteomyelitis of the tibia at the stages of its treatment using the method of transosseous distraction osteosynthesis.

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MATERIAL AND METHODS

Biochemical parameters of blood serum were studied in 15 patients with chronic posttraumatic osteomyelitis of the tibia. All patients underwent a two-stage treatment. At the first stage, sequester nectectomy of the lesion focus was carried out followed by osteosynthesis with the Ilizarov apparatus. At the second stage, compensation of the bone defect formed was produced by the formation of a distraction regenerate according to the Ilizarov method. To do this, osteotomy was performed in a healthy bone part of the segment followed by gradual distraction of the osteotomized fragment for elongation (rate: 0.25 mm, 3–4 times a day). A distraction regenerate was formed in the osteotomy site.

Depending on the bone defect size, the patients were divided into two groups. The defect size was from 3 to 5 cm in patients of the first group (n = 7, mean age 42.4 ± 6.9 years). In the patients of the second group (n = 8, mean age 37.5 ± 7.8 years) the size of the defect was from 7 to 12 cm.

Permission from the Ethics Committee of the *RISC for RTO* of the Ministry of Health of the Russian Federation was obtained to conduct this clinical study.

The concentrations of inflammatory indices such as C-reactive protein (CRP) and sialic acids (SA) was determined in the blood serum of patients at the stages of treatment. To assess bone metabolism, the activity of alkaline phosphatase (ALP) and tartrate-resistant (bone) acid phosphatase (TRAP) was determined in blood serum. Energy metabolism was assessed by the level of lactate in the blood, and the degree of damage to skeletal muscles was assessed by the activity of creatine phosphokinase.

The activity of the enzymes, as well as the concentrations of C-reactive protein and lactate in serum, was determined with an automatic biochemical analyzer Hitachi/BM 902 (F. Hoffmann – La Roche Ltd/ Roche Diagnostics GmbH) using reagent kits from Vital Diagnostic (Russia, St. Petersburg). Sets of reagents *Sialotest 100* (Russia, St. Petersburg) was used to study the concentration of sialic acids.

The parameters studied in the dynamics of treatment were compared with reference values obtained in the samples of blood serum collected from 16 practically healthy subjects, aged 25 to 45 years. The reliability of the differences between the parameters of the reference group and the values at the time-points of the study in the clinical groups was assessed using the Mann-Whitney T-test. The reliability of the intergroup differences of the studied indicators at the study points was determined using the nonparametric Kruskal-Wallis criterion, followed by a multiple comparison using the Dunn test. The data in the tables and in the graph are presented as median (Me) and interquartile range (25^{th} and 75^{th} percentile).

RESULTS

Before treatment, the studied serum levels were not significantly different between the groups, although the level of lactate (L), creatine phosphokinase (CP) and sialic acids was statistically significantly higher than the mean values of the reference group. Calculation of correlation coefficients of these indicators with the size of the defect did not reveal significant values (**Table**).

At the treatment stages, the dynamics of alkaline phosphatase activity in the groups was similar. No significant changes were observed between the groups. Thereby, the activity of the enzyme did not exceed the values of the reference group (**Fig. 1**). In turn, the activity of TRAP in both groups increased relative to the reference norm by the days 21-30 at the first stage of treatment and decreased to the values of the reference group by the beginning of distraction.

The activity of creatine phosphokinase significantly increased in both groups only on the 3rd day after the operation relative to the reference level but returned to the norm already on the 21st day of treatment (**Fig. 2**). The concentration of lactate in the serum in both groups was significantly higher than the values of the reference group at all time-points of the observation. There were no significant differences between the groups for these indicators.

Table

Several biochemical parameters of blood serum in patients of the examined groups before the beginning of treatment, Me (25^{th}÷75^{th} percentile)

Groups	ALP, U/l	TRAP, U/l	L, mmol/l	CP, U/l	CRP, мг/л	SA, mmol/l
Reference	80 (56 ÷ 103)	4.20 (3.0÷4.90)	1.92 (1.50 ÷ 2.33)	75 (51 ÷ 105)	1.0 (0 ÷ 8)	3.05 (2.45 ÷ 3.95)
Group 1	93 (91 ÷ 139)	3.80 (3.4÷4.3)	3.10* (2.72 ÷ 3.81)	122* (78 ÷ 131)	9.0 (1.0 ÷ 26.0)	4.64* (2.44 ÷ 5.45)
Group 2	94 (84 ÷ 104)	4.35 (3.65÷5.3)	2.70* (2.41 ÷ 3.12)	129* (83 ÷ 176)	6.9 (0.5 ÷ 24.1)	4.29* (3.42 ÷ 5.95)

Note: * – significant differences from reference values by $p< 0.05$.

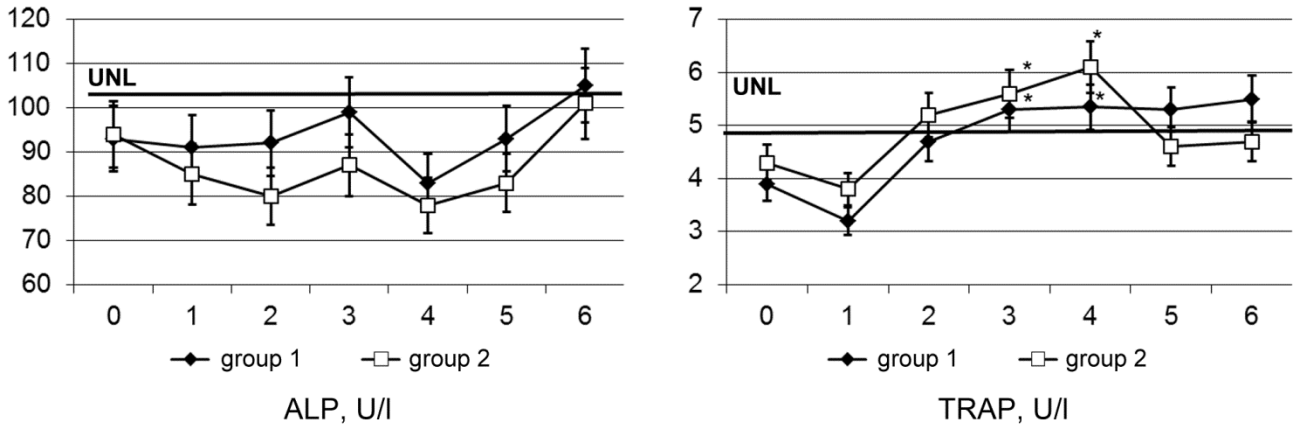

Fig. 1 Dynamics of changes in phosphatase activity at the treatment stages in patients of the examined groups. Note: * – differences in comparison with the reference group are significant with $p < 0.05$. On the OX axis - treatment time-points: 0 - before treatment; 1 – 3^{rd} day of fixation; 2 – 7^{th} day of fixation; 3 – 21^{st} day of fixation; 4 – 30^{th} day of fixation; 5 – the beginning of distraction; 6 – the end of distraction. UNL - upper normal level (reference values)

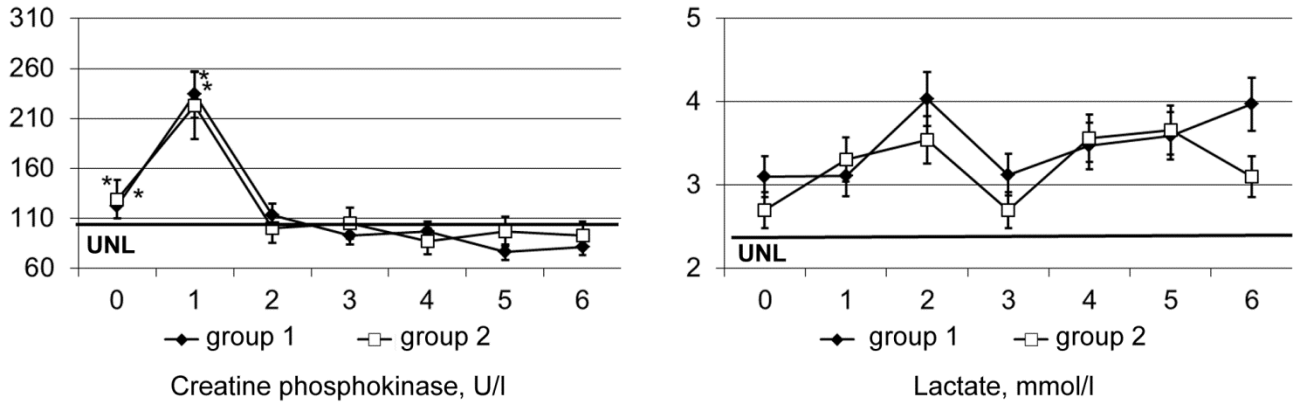

Fig. 2 Dynamics of changes in the activity of creatine phosphokinase and lactate concentration at the stages of treatment in patients of the examined groups. Note: * – differences in comparison with the reference group are significant with $p < 0.05$. On the OX axis – treatment time-points: 0 – before treatment; 1 – 3^{rd} day of fixation; 2 – 7^{th} day of fixation; 3 – 21^{st} day of fixation; 4 – 30^{th} day of fixation; 5 – the beginning of distraction; 6 – the end of distraction. UNL – upper normal level (reference values). All values for lactate are significantly different from the reference group with $p < 0.05$

The concentrations of CRP and sialic acids at the first stage of treatment were significantly increased in patients of both groups relative to the reference norm (**Fig. 3**). Significant intergroup differences were noted for sialic acids: in patients of the second group, the concentration of this metabolite was higher than the values of group 1 and the reference group. Nevertheless, by the beginning of the second stage, the level of CRP and sialic acids did not differ significantly from the norm.

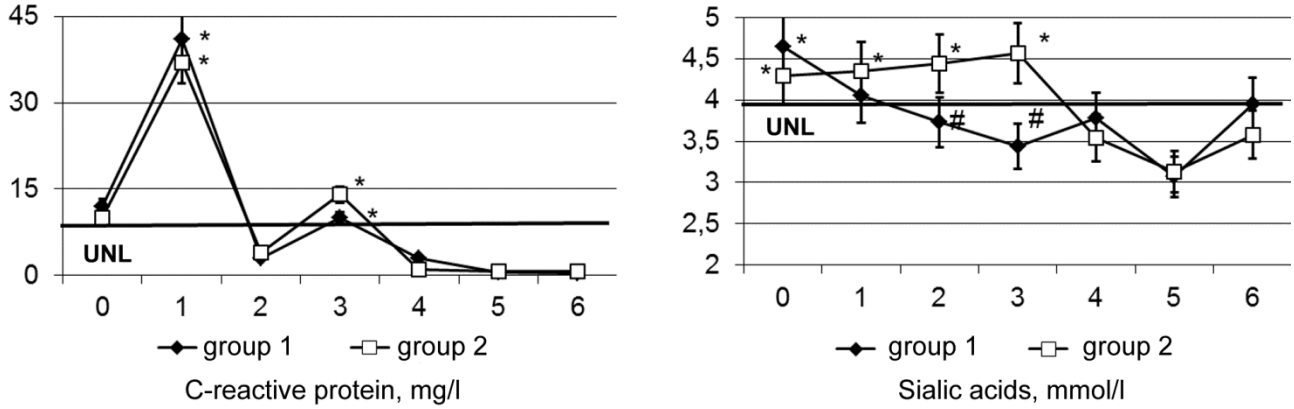

Fig. 3 Dynamics of changes in the concentration of C-reactive protein and sialic acids at the stages of treatment in patients of the examined groups. Note:* – differences in comparison with the reference group are significant with $p < 0.05$; # – significant differences between the groups with $p < 0.05$. On the OX axis - treatment time-points: 0 – before treatment; 1 – 3rd day of fixation; 2 – 7th day of fixation; 3 – 21st day of fixation; 4 – 30th day of fixation; 5 – the beginning of distraction; 6 – the end of distraction. UNL is upper normal level (reference values)

DISCUSSION

An analysis of the dynamics of changes in the biochemical parameters of blood serum studied in patients of the examined groups makes it clear that the magnitude of the shifts of these markers is practically independent of the bone defect size, both before the beginning and at the stages of treatment. It was noted that only the concentration of sialic acids correlated with the size of the bone defect at certain periods. Its growth was higher in the patients of the second group on days 7-21 of fixation than in the patients of the first group. However, by the time of the second stage of treatment (distraction), the level of this metabolite, like the content of other indicators, was within the norm.

In this regard, only those indicators that were significantly higher than the values of the reference group before the start of treatment and at the first stage and then recovered to the norm at the beginning of the second stage can be of diagnostic value. According to our study, such factors include the activity of TRAP, the levels of CRP and sialic acids. Considering that one of the signs, on the basis of which the second stage of treatment (the beginning of lengthening) started in the examined patients, was the normalization of hematological parameters (total blood count), the above criteria can be included as additional tests for the step-by-step monitoring of treatment in patients with osteomyelitis with the use of transosseous osteosynthesis. In particular, the activity of TRAP, concentrations of CRP and sialic acids within the limits of the norm can be attributed to the signs on the basis of which it is possible to start distraction - the second stage of treatment in patients with chronic osteomyelitis of the tibia with the Ilizarov method. The recovery of these parameters indicates that the osteomyelitic focus has been cleaned and osteolytic activity decreased.

CONCLUSION

Thus, summarizing the obtained data, it is possible to single out a group of laboratory tests (bone isoenzyme of acid phosphatase, C-reactive protein and sialic acids) for evaluating the effectiveness of a step-wise treatment in patients with posttraumatic osteomyelitis at its periods of restorative treatment which along with clinical laboratory (hematological) tests can be included in the assessment of the onset time for a bone lengthening stage or the beginning of the distraction.

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