Original Article

New laboratory tests for evaluating the effectiveness of the method of transosseous osteosynthesis for treatment of patients with chronic osteomyelitis of the foot bones

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Abstract

Introduction The use of laboratory tests to monitor the treatment of patients with chronic osteomyelitis has a lot of clinical relevance. **The purpose** of the study was to identify laboratory tests for assessing metabolic processes in patients with purulent lesions of the foot bones for monitoring the dynamics of the recovery processes in the course of treatment. **Methods** The studies were carried out in 36 patients with chronic osteomyelitis of the calcaneus and adjacent bones of the foot of traumatic etiology. All patients were treated with the method of the Ilizarov transosseous osteosynthesis. Biochemical and coagulation parameters were studied. **Results** It was found that in patients with purulent lesions of the foot bones, the elevated levels of blood serum lactate were most frequently detected before surgery (52.8 %, 95 % CI: 36.6-68.6). The incidence of elevated CRP was 27.7 % (95 % CI: 14.6-43.3) on average, and one third of patients had elevated fibrinogen levels (33.3 %, 95-CI: 19.1-49, 3). During the treatment period, the incidence of elevated lactate levels in patients did not change but the incidence of elevated CRP levels increased significantly which was observed in 77.8 % of patients on the 3rd post-surgery day. By discharge from the hospital, elevated values of CRP and lactate occurred in 11.1 % of patients. It is assumed that the greatest diagnostic significance is the assessment of the level of lactate in the dynamics of the treatment in target patients. **Discussion** Based on the results of the studies, a laboratory sign was found that indicates the effectiveness of surgical treatment in patients with chronic osteomyelitis of the foot bones using the method of transosseous osteosynthesis. Such a sign is a decrease in the initially elevated concentration of lactate in the blood serum of patients in the postoperative period. The detected sign meets the requirements for its applicability in laboratory tests: 1) this sign is the most common in the target group of patients; 2) the dynamics of changes in the level of lactate correlates with the ongoing treatment; 3) this test is an indicator of a significant physiological process: oxidative metabolic processes in patients with the studied pathology.

Keywords: chronic osteomyelitis, foot bones, laboratory diagnostics, transosseous osteosynthesis, Ilizarov method

INTRODUCTION

Management of chronic osteomyelitis is one of the most difficult challenges in the current orthopedic practice, both in clinical medical and social terms [1–5]. The multi-factorial nature of this disease requires several stages of surgical interventions combined with long courses of antibiotic therapy and a subsequent long rehabilitation period [6–10].

Under these conditions, to monitor the process of bone tissue restoration in the osteomyelitis nidus and assess the intensity of suppression of systemic and local inflammatory processes becomes an urgent problem to prove the effectiveness of its treatment [11–14]. The available works demonstrate that the main points of growth regarding the monitoring of the treatment in osteomyelitic disease are the development of protocols of laboratory tests [15], the main characteristics of which is the possibility of preclinical evaluation of the treatment process in this pathology [16]. However, it is obvious that to date, specific strategies for applying laboratory diagnostic criteria in the treatment of such patients have been poorly defined [17].

In terms of expanding the range of laboratory tests applicable to assess the effectiveness of the treatment of patients with chronic osteomyelitis, the fact is that a significant role has been given recently to secondary systemic metabolic disorders (oxidative stress, intoxication, local hypoxia) in the pathogenesis of this disease that develop as a result of generalization of the main process [18, 19]. Therefore, the laboratory tests that allow evaluation of such metabolic disorders may be useful as additional criteria for monitoring the treatment of patients with chronic osteomyelitis.

Purpose To study the laboratory tests to assess metabolic processes in patients with purulent lesions of the foot bones to solve the problems of dynamic monitoring the recovery processes in the course of treatment.

MATERIAL AND METHODS

In order to standardize the results of the study, we chose 36 patients with chronic osteomyelitis of the calcaneus and adjacent foot bones of traumatic etiology as the target group. At admission to the clinic, the age of the patients varied from 25 to 58 years (mean age 46 ± 11 years), the duration of the disease ranged from

1 to 10 years. All patients were previously repeatedly treated both conservatively and surgically at other medical institutions. However, the treatment did not result in a stable remission of the purulent process.

All patients included in the study underwent debridement of the osteomyelitic nidus by radical sequestrectomy followed by orthopedic reconstruction of the bones, joints, and tendon-ligamentous apparatus of the affected segment with the Ilizarov method. The choice of the scope of surgical intervention, segment fixation options, orthopedic correction, antibiotic therapy, infusions and detoxification therapy was based on the nature and location of the purulent inflammatory process, and also considered patient's age, soft tissue condition, radiography, MSCT, and microbial tests. Anticoagulation therapy was mandatory in order to prevent postoperative thromboembolic complications. Antibacterial therapy was based on the sensitivity of the microflora, was initiated on the 1st day after surgery and continued from 7 to 15 days (averaged 12 days). The osteomyelitic process was arrested in all patients included in the study during treatment. The results of infection suppression was based on the system proposed by the international multidisciplinary consensus basis [20].

The objects of the study were serum and blood plasma, as well as daily urine of patients. Samples for tests were taken before the operation, on the 3rd and 15th days after the operation, and also before discharge from the hospital.

The findings of the laboratory tests of 19 practically healthy subjects aged 30 to 50 years (mean age 43 ± 7 years) were used as reference values.

This clinical study was approved by the ethics board of the Ilizarov NMRC for TO of the RF ministry of health.

The levels of total and C-reactive (CRP) protein, glucose, total cholesterol, triglycerides, urea, creatinine, lactate (lactic acid, LA), potassium, sodium, chlorides, total calcium, magnesium, inorganic phosphate were checked in the blood serum of the patients at the study time-points. The activity of enzymes was determined: alkaline phosphatase (ALP), tartrate-resistant (bone) acid phosphatase (TrAP), creatine kinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (AlAT) and lactate dehydrogenase (LDH). The concentration of calcium and inorganic phosphate was determined in daily urine.

The activity of enzymes, as well as the levels of C-reactive and total protein, glucose, total cholesterol, triglycerides, urea, creatinine, lactate, total calcium, magnesium, inorganic phosphate in blood serum, calcium and inorganic phosphate in daily urine were determined with an automatic biochemical analyzer Hitachi/BM 902 (F. Hoffmann-La Roche Ltd./Roche Diagnostics GmbH) using Vital Diagnostic reagent kits (Russia, St. Petersburg). The content of sodium, potassium and chlorides was determined by the ion-selective method on the ion-selective block of the Hitachi/BM 902 biochemical analyzer.

Coagulogram indicators were studied in blood plasma: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time, fibrinogen level. Coagulation studies were performed with an automatic coagulometer ACL TOP (Instrumentation Laboratory).

The results of the study are presented in Tables 1, 2 and 4 as arithmetic means and standard deviations (Xi ± SD), and in Table 3 as absolute values, percents and 95 % confidence interval (95 % CI). The normality of the distribution of samples was determined using the Shapiro-Wilk test. The significance of differences between the values of patients' indicators before treatment and at the treatment time-points was compared with the values of the reference group. Additionally, the indicators at the treatment time-points were compared with baseline values (before treatment). The procedure for statistical assessment of the significance of differences in the indicators within the study groups (before/after treatment) was performed using the Wilcoxon W-test. The Mann-Whitney T-test was used to assess the statistical significance of indicators between the groups. Statistical analysis of the significance of differences between the groups in terms of qualitative criteria (occurrence of signs given in Table 3) was performed using the χ^2 test. The minimum significance level (p) was taken equal to 0.05.

<div align="center">RESULTS</div>

Changes in biochemical and coagulation parameters in the dynamics of treatment are presented in Tables 1 and 2. It was found that before the start of treatment, statistically significant differences in the studied laboratory parameters relative to the reference values were revealed only for three markers: CPK, lactate and fibrinogen. In the dynamics of treatment, the average values of these indicators decreased. In the postoperative period, the level of CRP in the blood serum increased significantly. For other laboratory tests, one-time elevations were noted at certain periods of the study without any regularity.

Based on the dynamics of changes in laboratory tests described above, the identification of the tests that could indicate the effectiveness of the treatment is complicated by the fact that the deviations present in patients before treatment were superimposed by the changes caused by surgery and concomitant therapy. Therefore, in order to identify the most informative markers, we considered only those indicators, which values significantly changed relative to the norm before treatment, i.e. lactate and fibrinogen. In addition, the level of CRP was additionally considered as the most commonly used test to assess the severity of the inflammatory process.

Table 1

Dynamics of biochemical parameters of blood serum and daily urine in patients with purulent lesions of the foot bones at the time-points of treatment (Xi ± SD)

Parameter	RG	Before surgery	Day 3 post-surgery	Day 15 post-surgery	At discharge
Blood serum					
ALP, U/l	81 ± 18	90 ± 30	98 ± 25	103 ± 24	104 ± 9*
ТрКФ, Е/л	4.25 ± 1.32	4.30 ± 1.90	3.70 ± 1.21	5.30 ± 1.27	4.90 ± 1.01
Total calcium, mmol/l	2.44 ± 0.14	2.34 ± 0.13	2.32 ± 0.10	2.35 ± 0.16	2.50 ± 0.12
Phosphate, mmol/l	1.21 ± 0.18	1.18 ± 0.15	1.26 ± 0.15	1.26 ± 0.05	1.52 ± 0.19*
Magnesium, mmol/l	0.90 ± 0.10	0.86 ± 0.05	0.77 ± 0.05$^+$	0.77 ± 0.05$^+$	0.85 ± 0.09
Total protein, g/l	72 ± 7	74 ± 5	68 ± 4$^+$	73 ± 5	74 ± 7
CRP[#], mg/l	0.5 (0÷1.5)	2.4 (0÷40)	33.2 (0÷100)*	2.2 (0÷11)	2.1 (0÷6)
Urea. Mmol/l	5.10 ± 1.11	5.24 ± 1.02	4.13 ± 1.60	4.37 ± 1.27	4.26 ± 1.61
Glucose, mmol/l	5.05 ± 0.45	5.25 ± 0.34	5.29 ± 0.35	5.02 ± 0.42	4.89 ± 0.48
Lactate, mmol/l	1.90 ± 0.35	2.27 ± 0.28*	2.42 ± 0.12*	2.54 ± 0.18*	1.88 ± 0.48
LDH, U/l	321 ± 40	286 ± 45	304 ± 59	300 ± 55	323 ± 35
CPK, u/l	69 ± 20	101 ± 32*	195 ± 90*	55 ± 20	40 ± 14
AlAT, u/l	19 ± 9	25 ± 9	29 ± 13	42 ± 19*	14 ± 8
AcAT, u/l	18 ± 8	20 ± 7	28 ± 11	28 ± 12	14 ± 6
Creatinin, mcmol/l	88 ± 15	92 ± 27	89 ± 22	93 ± 20	84 ± 10
Triglycerides, mmol/l	1.62 ± 0.51	1.87 ± 0.78	1.19 ± 0.50	1.54 ± 0.53	1.97 ± 0.61
Cholesterol, mmol/l	5.95 ± 1.31	5.63 ± 1.18	4.85 ± 1.33	4.21 ± 1.09	4.93 ± 0.25
Sodium, mmol/l	141 ± 8	141 ± 3	142 ± 3	141 ± 4	141 ± 4
Potassium, mmol/l	4.45 ± 0.45	4.40 ± 0.45	4.31 ± 0.47	4.78 ± 0.41	4.52 ± 0.16
Chloride, mmol/l	107 ± 6	107 ± 4	104 ± 4	103 ± 5	112 ± 5
Urine					
Ca, mmol/d	2.92 ± 1.42	3.95 ± 1.70	4.06 ± 2.08	3.92 ± 0.97	1.91 ± 0.29
P, mmol/d	26 ± 9	19 ± 10	19 ± 8	13 ± 6*	21 ± 7

Note * – differences are significant with the reference group (RG) at a significance level of $p < 0.05$; $^+$ – differences at treatment time-points are significant with preoperative at $p < 0.05$; [#] – the distribution of this indicator differed from the normal one, therefore this indicator is presented as a median (minimum ÷ maximum value)

Table 2

Dynamics of coagulation parameter in patients with foot bone infection at time-points studied (Xi ± SD)

Parameter	RG	Before surgery	Day 3 post-surgery	Day 15 post-surgery	At discharge
APTT, sec	30.8 ± 4.7	34.4 ± 3.8	35.1 ± 4.9	31.2 ± 3.9	32.2 ± 5.0
PT, sec	11.0 ± 1.1	12.7 ± 1.8	13.0 ± 1.2	12.5 ± 1.4	10.9 ± 1.1
Thrombin time. sec	16.4 ± 2.2	17.6 ± 1.3	17.9 ± 2.0	18.4 ± 0.9	15.7 ± 1.9
Fibrinogen, g/l	3.0 ± 0.8	4.5 ± 1.0*	4.2 ± 0.8*	3.8 ± 0.7	3.4 ± 1.0

Note * – differences are significant against the reference group (RG) at $p < 0.05$

The informative value of the selected tests for the analysis of the effectiveness of treatment in patients with chronic osteomyelitis of the foot during the treatment period was calculated based on the assessment of the frequency of changes in each of the indicators. A positive result, indicating a metabolic disorder caused by the osteomyelitis process, was an increase in the value of each indicator relative to the norm. Data on the positive results of the selected tests are presented in Table 3.

Table 3

Incidence[#] of positive results of certain laboratory tests in patients with foot bone infection at the time-points studied

Test values	Before surgery	Day 3 post-surgery	Day 15 post-surgery	At discharge
CRP > 10 mg/l	10/36 **27.7** (14.6–43.3)	28/36 **77.8*** (63.0–90.0)	7/36 **19.4** (8.4–33.8)	4/36 **11.1** (3.1–23.2)
MK > 2.2 mmol/l	19/36 **52.8** (36.6–68.6)	20/36 **55.6** (39.3–71.2)	18/36** **50.0** (34.0–66.0)	4/36* **11.1** (3.1–23.2)
Fibrinogen > 4.0 g/l	12/36 **33.3** (19.1–49.3)	9/36** **25.0** (12.4–40.2)	5/36 **13.9** (4.7–26.9)	3/36 **8.3** (1.7–19.4)

Note * – differences are significant with preoperative indicators at a significance level of $p < 0.05$; ** – differences between the indicators are significant at the time-points at $p < 0.05$; [#] – results are presented in absolute values (number of patients with a positive test result / total number of patients examined) and percentage of the total number (95th confidence interval).

It was found that the elevated serum lactate values were most common in the patients with purulent lesions of the foot bones before surgery, (52.8 %, 95-CI: 36.6-68.6). The incidence of elevated CRP was lower and averaged 27.7 % (95-CI: 14.6-43.3), and the level of fibrinogen was elevated in one third of patients (33.3 %, 95-CI: 19.1-49.3). The differences between the indicators were not statistically significant.

At the treatment time-points, the rate of elevated lactate levels in patients did not change, the incidence of elevated CRP levels increased significantly (on the 3rd day after surgery in 77.8 % of patients). However, after the end of treatment, the elevated values of CRP and lactate were observed in 11.1 % of patients. The occurrence of elevated fibrinogen levels significantly decreased during treatment. However, we considered the use of this test to assess metabolic processes in patients with purulent lesions of the bones of the foot to be incorrect, because changes in this indicator reflect the effectiveness of anticoagulation therapy. This observation, however, also has its clinical implications.

In general, evaluating the total results presented above, the dynamics of changes in the level of lactate in the blood serum of the patients looks most indicative. This test meets the following important criteria for the applicability of laboratory tests for monitoring tasks: 1) an increase in lactate relative to the norm is the most common symptom in the target group of patients; 2) the dynamics of changes in the level of lactate correlates with the ongoing treatment: the level was increased before treatment, decreased at the time of discharge.

In addition to the requirements presented, the third criterion for the applicability of the laboratory test should be an indicator of a sufficiently significant physiological process and have a sensible and functional interpretation for this group of patients. For these purposes, we evaluated the main clinical and demographic data of the patients, who were divided into two groups: a group of patients whose lactate level was within the normal range before surgery and a group of patients whose lactate level was above the upper limit of the normal range (Table 4).

It was found that statistically significant differences between the groups were related to the duration of the disease, which was longer in patients with elevated lactate levels. This observation allows us to conclude that the elevation in lactate in patients with chronic osteomyelitis, associated with changes in oxidative metabolism, indicates a chronic process with the signs of metabolic acidosis. Sanitation of the osteomyelitic nidus leads to the relief of metabolic disorders. It gives reason to interpret that the decrease in lactate levels in patients with its elevated values before surgery is a favorable sign of the ongoing treatment in terms of restoring oxidative processes in the tissues and organs of the affected segment. The fact that at the end of treatment, the osteomyelitic process was arrested in all patients, we can say that the decrease in the level of lactate in the patients with an initially (before surgery) elevated level may be attributed to the signs indicating an effective suppression of the inflammatory osteomyelitic process. We estimated the quantitative predictive value of a positive test result for isolated lactate reduction during treatment at 79.0 %.

Table 4

Clinical and demographic data of the examined patients, whose lactate level was within the normal range before surgery and of patients whose lactate level was above the upper limit of the normal range (Xi ± SD)

Groups	Age (years)	Disease duration (years)	M/F (%) gender
Normal lactate level before surgery (n = 17)	44.3 ± 11.9	3.8 ± 1.1	12/5 (70.5/29.5)
Higher that normal level of lactate before surgery (> 2.2 mmol/l (n = 19)	49.0 ± 11.0	5.1 ± 1.0*	12/7 (63.1/36.9)

Note * – differences are significant between the groups at p < 0.05.

DISCUSSION

The current studies on searching for laboratory tests able to assess the process of treating patients with osteomyelitis are mostly devoted to the development of the protocols for the use of the tests that characterize the inflammatory process to determine the effectiveness of its cessation as a sign of the effectiveness of the treatment (immunological status, ESR, CRP) [21–24]. In addition to the above tests, a separate direction is a search for new markers for solving the above problems [25–27]. However, a low diagnostic sensitivity and accuracy of these indicators limit the use of such tests [28].

Among the indicators for evaluating the oxidative processes, changes in which are one of the elements of the secondary changes in the pathogenesis of chronic osteomyelitis, the markers to assess oxidative stress (protein and lipid peroxidation) have been studied [29–33]. Undoubtedly, the set of tests proposed in these works enables to effectively assess the oxidant-prooxidant balance in patients with chronic osteomyelitis. However, these markers have limitations as it is not possible to evaluate the metabolic oxidative status, and the tests themselves are not unified and standardized. Thus, it

is impossible to use them in routine clinical practice. Moreover, these tests, used for laboratory assessment of metabolic disorders in chronic osteomyelitis including purulent inflammatory lesions of the foot bones, do not show acceptable diagnostic sensitivity.

Therefore, we have proposed a new test that corresponds not only to the pathophysiological features of the course of chronic osteomyelitis, but is also an accessible test for routine practice. The diagnostic sign in cessation of the secondary disorders of oxidative metabolism in patients with chronic osteomyelitis is the recovery of normal values of elevated lactate levels during treatment. The measurement of lactate level is an accessible test for laboratories of different levels, the analysis itself is unified, standardized, and the reagents are registered for *in vitro* diagnostics. Moreover, this sign (an elevated level of lactate and its decrease during treatment) has found a similar application in the diagnosis and prognosis of complications after skeletal injuries [34]. It should be noted that the determination of the level of lactate in the blood serum of patients with chronic osteomyelitis enables to evaluate the link in the pathogenesis of chronic osteomyelitis which was previously not sufficiently evaluated by other authors and proposed for the tasks of monitoring. The probable advantage of the test proposed by us is also the fact that this technology can provide an earlier diagnosis of systemic disorders in target patients, since a decrease

in lactate level, being a secondary sign in relation to primary etiotropic factors, appears before a decrease in the level of CRP, ESR and other laboratory tests for assessing inflammatory processes.

Undoubtedly, the limitation of this study should be recognized. The studied laboratory tests can only be used for patients with chronic osteomyelitis of the foot bones and it is not obvious that similar results may be obtained for osteomyelitis of other location. Therefore, clinical validation of the use of the proposed by us diagnostic technology is required.

In the context of the current clinical practice, it seems that more popular tests such as CRP and ESR may be quite sufficient to assess the arrest of the inflammatory process in patients with osteomyelitis; however, given the pathogenesis of the disease and the available work on the insufficiency of using isolated laboratory tests, we believe that additional laboratory evaluation of the entire set of pathophysiological mechanisms, along with the existing ones, will improve the efficiency of monitoring this disease. An important step in this direction is to improve the diagnostic accuracy of the laboratory tests for the effectiveness of the treatment in chronic osteomyelitis based on the combination of laboratory criteria, including those proposed by us, into one diagnostic profile. The creation of such protocols is an important trend in the diagnosis of osteomyelitis [35, 36].

CONCLUSION

Thus, we have found a laboratory sign that testifies the effectiveness of surgical treatment in patients with chronic osteomyelitis of the foot bones with the method of transosseous osteosynthesis. Such a sign is a decrease in the initially elevated level of lactate in the blood serum of patients in the postoperative period.

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