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Prediction and control of the distraction osteogenesis course. Analytical review

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This review analyzes and assesses the existing methods and approaches to prediction and control of the course of distraction osteogenesis (DO). The analysis of the literature revealed few works that recommended specific predictors or methods for prognosis of the course of distraction osteogenesis at the stages of limb lengthening. The authors identified some diagnostic criteria for assessing the distraction regenerate as potential criteria for predicting its development and maturation. It was found that all available predictors and potential diagnostic criteria for assessing the state of the distraction regenerate in clinical practice are used to further correct the distraction regime (respectively, at the stage of distraction) and to determine the timing of the removal of the apparatus, as well as prognosis of recurrence, fracture, and deformity of the regenerate in the non-apparatus period. It was shown that all known diagnostic methods can be applied for the assessment and prediction of the DO course: radiological, physiological, ultrasound diagnostics, laboratory tests. It is stated that a quantitative assessment of the informative value of most of the known predictors of DO disorders is necessary from the point of view of the evidence-based medicine. Difficulties and problems of the development and application of prognostic tests for assessing DO are described. The directions to the development of this topic are proposed. Predicting the DO course is an essential element for monitoring the tissue repair of the segment under lengthening. Prediction and subsequent prophylaxis of DO disorders is a promising solution for optimizing and improving the quality of treatment of patients with orthopedic diseases by using the Ilizarov method of transosseous distraction osteosynthesis.

Keywords: distraction osteosynthesis, Ilizarov method, limb lengthening, prediction

The method of transosseous distraction osteosynthesis (TDO), the fundamental justification and practical use of which were developed by G.A. Ilizarov, enables to achieve significant lengthening of long bones and simultaneous correction of their deformities [1–2]. One of the identified problems in its application is control and management of distraction osteogenesis (DO) [3], which include the diagnosis of the state of distraction regenerate (DR). Mainly radiographic study is used for this purpose followed by, if necessary, correction of treatment tactics. Such a practice, in fact, is just stating the fact and does not allow predicting and preventing possible disturbances in the DO course [4–5]. To solve this problem, an analysis of existing methods for predicting the DO state in clinical practice is necessary. The development of this direction, in our opinion, would enable to qualitatively improve the results of TDO treatment. In addition, this logically fits into the current preventive, predictive and personalized paradigm in contemporary medicine (or 4P medicine) [6].

In connection with the tasks outlined, we conducted an analytical review of the available literature with the aim of assessing the development of the topic on the possibilities and methods for predicting the DO course in clinical practice with the use of the TDO method.

Literature search strategy Open electronic databases of scientific literature PubMed and eLIBRARY were searched for with the keywords: *distraction osteosynthesis, distraction osteogenesis, prognosis, prediction, Ilizarov method, Ilizarov* (in Russian and English versions). The search used separate words and their combination.

To analyze and evaluate the literature data, criteria were determined for including and excluding the sources into the analytical study.

Inclusion criteria

1. Full-text sources or structured abstracts with specific quantitative data

2. Clinical studies indicating that patients were treated using TDO techniques

3. In the sources, distraction regenerate should be evaluated using the characteristics described by quantitative findings

Exclusion criteria

1. Case reports, abstracts of presentations

2. Studies with "duplication" (similar study protocol, groups and number of patients, etc.). Among "duplicate" articles, a more recent source was chosen.

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RESULTS

Literature analysis revealed a small number of works that recommended specific predictors or methods for predicting the course of distraction osteogenesis at the stages of limb bones lengthening with the TDO method.

Therefore, we also included in the analysis those works where the authors proposed quantitative criteria for assessing DO, which are potential predictors for the DO.

A total of 40 sources were included in the analysis [7–46].

The assessment shows that all available predictors and potential diagnostic criteria for evaluating the DO in clinical practice are used mainly for two purposes:

– to correct the distraction mode. In clinical practice, after specific signs indicating a disorder or an increase in the risk of possible DO disorders, as a rule, correction of the distraction regime and/or the use of any additional means (pharmacological correction, physiotherapeutic or other means) should follow. A positive outcome for such preventive measures is achievement of the magnitude of lengthening planned;

– to determine the time-point for removal of the apparatus, the prognosis of recurrence, fractures and regenerate deformity in the period after the removal of the apparatus. Preventive measures at this stage, as a rule, are associated with procedures for stimulating regeneration maturation, and their positive outcome is a decrease in the frequency of recurrence, deformities, fractures of the regenerate.

Based on this, we grouped the literature published depending on the goals of prognosis.

The methods for DO assessment and prediction in the period of distraction are summarized in Table 1. The table shows that practically all existing diagnostic methods can be applied for the purpose of assessing and predicting the DO course: radiological, ultrasound, laboratory and physiological tests. At the same time, the analysis of these works suggests that laboratory tests (possibility of prediction before surgical treatment and during the first 3–4 days of distraction) and ultrasound diagnosis (the first weeks of distraction) can be classified as the earliest preclinical and pre-roentgenological predictors of DO disturbance.

To assess DR in order to predict abnormalities after removal of the apparatus, the methods of radiological assessment were mainly used: CT, MRI, and bone mineral density (BMD) (Table 2). There are methods of laboratory assessment and prediction of the DR maturation in the period of fixation and in the period after removal of the apparatus.

Table 1

Methods and criteria for assessing and predicting the state of distraction regenerate during the distraction period

Method	Criteria, signs, objects of control	Reference list number
Radiography*	Quantitative DO evaluation, zonography, evaluation of optical density	7, 8, 9, 10
	Height of the connective tissue layer of distraction regenerate	11, 12
	DR shape	13
Ultrasound	DR Echographic signs	14, 15, 16, 17, 18
Physiological	Podography	19
	Thermography	20
Laboratory	Immunogram	21, 22
	Growth factors	23, 24, 25, 26, 27
	Blood biochemstry	28, 29
	Hemostasis	30
	Hematology	31

Note: * – only quantitative signs were taken into account, qualitative (descriptive) signs were not taken into account

Table 2

Methods and criteria for assessing and predicting the state of distraction regenerate at the fixation stage and in the non-apparatus period

Diagnosis method	Criteria, signs, objects of control	Reference list number
Radiography	Quantitative DO evaluation, zonography, evaluation of optical density	7, 8, 9, 32, 33, 34, 35, 36
	DR Density, diameter, shape	37, 38, 39, 40
	DK BMD	41, 42
MRI	Density of the cortical plate	43
Laboratory test	Blood biochemistry	44, 45, 46

Thus, the data presented allow us to conclude that, there are enough methods for DR assessment to control the DO course. Many of these methods are quite suitable for solving the problems of the DO development prognosis.

However, from the perspective of evidence-based medicine, for most of the tests presented above, a quantitative assessment of the information on these predictors is necessary (calculation of the odds ratio, sensitivity, specificity). The works in which this quantitative procedure was performed for the proposed criteria and tests are single; all sources are presented in Table 3. It is obvious that the data presented contain tests with a rather high predictive value [38, 40]. However, there are very few validated tests for predicting the DO course during lengthening of limb bones with the Ilizarov method.

Table 3

Value of some criteria for assessing the state of distraction regenerate at the stages of surgical treatment

Method	Predictor	Test value*	Reference
Radiography, DR shape	DR deformity	OR = 5.4 (95 % CI: 2.4–12.4)	[13]
Radiography, DR shape	DR fracture	OR = 19.3 (95 % CI: 2.9-128.0)	[38]
Radiography, DR density and diameter	DR deformity	Sensitivity 93.3 %; Specificity 83.2 %	[40]
Immunogram	DO delay	Prognostic accuracy 81.2 %	[21]

Note: * - as indicated in the sources; 95 % CI – 95 % confidence interval

DISCUSSION

The analysis of the literature data shows that currently there are enough methods and means for DR control, but the validated methods and criteria for predicting its state are single.

In addition to absence of reliable methods for predicting DO course, applicable in practice, there are a number of other difficulties in the development of this direction of diagnosis:

a) laboratory tests that seem attractive due to the possibility of early diagnosis are currently not unified and verified, therefore they are used only for research purposes;

b) it is necessary to distinguish between the concepts of diagnosing the current DR state and of its further condition. In practice, it is important for the clinician to understand that the prognosis is based on current diagnostic signs, which only with a certain probability can indicate possible disturbances in the further DO course.

c) the task which follows from the previous paragraph: what are the values of the sensitivity of the tests (odds ratio, specificity, etc.) that are acceptable for predicting adverse events or outcomes when applying the TDO method in clinical practice.

Therefore, in order to improve technologies, methods and prediction criteria for the tasks of DO control, we have identified a number of directions for their development.

1. The search for new sensitive predictors, mainly laboratory ones (molecular genetic and metabolic studies, etc.).

2. Mandatory unification and validation of potential prognostic tests.

3. Development of comprehensive assessment criteria and DO prediction using several study methods. The application of such approaches was found in a number of works [47, 48].

4. Expansion of prognostic abilities due to the development of technical methods for evaluating, analyzing and prognosis (mathematical modeling, neural networks, software and specialized "diagnostic gadgets" for the Ilizarov apparatus, etc.). Several approaches to the development of this direction were reported in literature sources [49–52].

It is worth noting that the DR evaluation is not the only objective of control and prognosis during surgical lengthening of limb bones with the Ilizarov method. In particular, numerous studies have shown the need and the ability to assess and predict the condition of skeletal muscles and nerves of the segment under lengthening [53–57], blood flow in the segment [58], as well as the prognosis of possible inflammatory reactions associated with the presence of metal implants [59]. Therefore, a comprehensive assessment and prediction of the DO course requires a systematic study considering the state of periosseous organs.

Thus, in terms of developing the direction of DO control and management in the short term, in our opinion, the priority is to validate the known

criteria in order to determine their prognostic value. In the long term (due to the expansion of the number of probable prognostic tests, development of a comprehensive assessment of DR and paraosseous tissues), the solution of the problems requires creation of an automated (on-line) system for monitoring and predicting the DO course. Moreover, development of such a system is currently quite possible technically.

CONCLUSION

Predicting the DO course is a necessary element in solving the problems of monitoring the tissue repair in the segment lengthened with TDO method. Prediction and subsequent prevention of DO disorders in clinical practice are a promising approach for optimizing and improving the quality of treatment and its outcomes in orthopedic patients who are treated with the Ilizarov method. However, this area of study currently requires significant, primarily technical and statistical development.

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