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NEW DAY IN MEDICINE**

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## ПРОФИЛАКТИКА ПОСЛЕОПЕРАЦИОННЫХ ОСЛОЖНЕНИЙ У БОЛЬНЫХ СО СПОНДИЛОЛИСТЕЗОМ

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### ✓ Резюме

*Проведенная иммуномодулирующая профилактика привела к достоверной положительной динамике ключевых иммунологических показателей, участвующих в патогенезе соответствующих нарушений при развитии послеоперационных осложнений после транспедикулярной фиксации позвонков у больных со спондилолистезом*

*Ключевые слова: спондилолистез, транспедикулярная фиксация позвонков, иммуномодуляция*

## SPONDILOLISTEZLI BEMORLARDA OPERACIYADAN KEYINGI ASORATLARNI PROFILAKTIKASI

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### ✓ Rezyume

*O'tkazilgan immunomodulyatsion profilaktika spondilolistezli bemorlarda umurtqa transpedikulyar fiksatsiyasidan keyin operatsiyadan keyingi asoratlarni rivojlanishiza tegishli buzilishlarning patogeneza ishtirok etadigan asosiy immunologik parametrlarning ishonchli ijobiy dinamikasiga olib keldi*

*Kalit so'zlar: spondilolistez, umurtqalarning transpedikulyar fiksatsiyasi, immunomodulyatsiya*

## PREVENTION OF POSTOPERATIVE COMPLICATIONS IN PATIENTS WITH SPONDYLOLYSTHESIS

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### ✓ Resume

*The conducted immunomodulatory prophylaxis led to reliable positive dynamics of key immunological parameters involved in the pathogenesis of the corresponding disorders in the development of postoperative complications after transpedicular fixation of vertebrae in patients with spondylolisthesis*

*Keywords: spondylolisthesis, transpedicular fixation of vertebrae, immunomodulation*

### Relevance

The problem of diagnostics, treatment and prevention of complications after spinal surgeries, in particular during transpedicular fixation in patients with spondylolisthesis, has remained the subject of close attention of specialists in the field of neurosurgery, orthopedics and rheumatology over the past decades. In the world literature of recent years, updated clinical and morphological

characteristics of various forms of spondylolisthesis are presented, including an assessment of predictors of instability and pain syndrome, and indications for surgical treatment have been clarified (1,3,5,7). Improved methods of transpedicular fixation have been developed using minimally invasive technologies, three-dimensional planning and individualized implants.

At the same time, despite advances in neuroorthopedic surgery, the number of postoperative complications, especially in patients with high surgical risk, remains significant. Recent studies have shown growing interest in immune mechanisms mediating the development of infectious, inflammatory and degenerative complications after spinal surgery (2,4,6,8). It has been established that local and systemic inflammation that occurs in response to implantation is mediated by the activation of innate immune cells - neutrophils, macrophages and dendritic cells, accompanied by the secretion of proinflammatory cytokines, which can lead to impaired bone tissue repair. Impaired regulatory T cells and imbalance between the Th1/Th2/Th17 profile are accompanied by a decrease in antigen-specific tolerance and potentiation of autoimmune reactions. Matrix metalloproteinases expressed in response to surgical trauma promote degradation of the intercellular matrix and prevent implant engraftment into bone tissue. A number of studies have described the role of Toll-like receptors and activation of NF- $\kappa$ B signaling pathways in the induction of chronic inflammation around implants (9,11).

In foreign practice, the relationship between the patient's systemic immune status and the outcomes of spinal surgeries is actively studied. Data on the use of immunological biomarkers to predict the risk of complications are published (5,8,10). However, many studies are predominantly observational in nature, and prognostic algorithms integrating immunological parameters into risk assessment models are insufficiently presented. It should be noted that despite the availability of generalized information on inflammatory reactions to implants, integration of structures and the frequency of complications, there are practically no systematic studies devoted to the assessment of immune markers and their prognostic significance specifically in TPFП in patients with spondylolisthesis. The lack of data on the role of cellular and humoral immunity disorders in the development of both early (infectious-inflammatory) and late (aseptic, fibrous) complications remains especially relevant.

Thus, there is currently a scientific and clinical demand for comprehensive studies aimed at identifying immunological predictors of unfavorable outcomes of surgical treatment of spondylolisthesis using TPFП. The study of this problem opens up prospects for a personalized approach to patient management and the introduction of targeted immunomodulatory prophylaxis. The formation of an immunologically oriented model for predicting complications will contribute to: increasing the accuracy of assessing the risk of an unfavorable outcome; identifying high-risk patients for targeted immunomodulatory prophylaxis and therapy; increasing the effectiveness of surgical treatment and reducing the incidence of disability in patients with spondylolisthesis who have undergone TPFП.

**The aim of the study** is to develop methods for predicting and immunoprophylaxis of complications after transpedicular fixation of vertebrae in patients with spondylolisthesis.

### **Materials and methods**

The study was conducted within the framework of an observational comparative analysis, with subsequent stratification of patients by the level of risk of complicated course and assessment of the effectiveness of personalized immunomodulatory prophylaxis.

The total sample size was 146 people. The study included 126 patients with an established diagnosis of degenerative or isthmic spondylolisthesis who underwent TPFП, as well as 20 clinically healthy volunteers who formed the control group. All patients were monitored at the Bukhara Regional Multidisciplinary Medical Center and the immunology laboratory of the Bukhara State Medical Institute from 2021 to 2024. The sample structure provided for the distribution of patients into three main groups depending on the clinical course and the intervention received: patients with a favorable postoperative outcome without immunoprophylaxis (group 1, n = 59), with a complicated course without immunoprophylaxis (group 2, n = 32) and patients who received immunomodulatory prophylaxis (group 3, n = 35). The control group (n = 20) was formed from volunteers recognized as clinically healthy based on the results of a medical examination. The main purpose of including this group was to determine reference values of immunological parameters that were subsequently used to assess deviations in patients.

The distribution of patients by gender, age and level of spinal segment lesion was statistically comparable between the groups. The majority were patients aged 40-59 years, which corresponds to the epidemiological data on degenerative forms of spondylolisthesis. The gender composition in all subgroups was balanced, with a slight predominance of men. The typical localization of the lesion was at the levels of L4-L5 and L5-S1, in some cases there were combined forms involving several segments. Concomitant pathology was represented mainly by arterial hypertension (almost 40% of cases), obesity (about 25%) and type 2 diabetes mellitus (more than 11%), which reflects the typical comorbidity profile in patients with degenerative spinal lesions. The proportion of patients without concomitant diseases was approximately a quarter of the sample.

Patients were selected based on clearly defined inclusion and exclusion criteria, which allowed for a homogeneous and reproducible sample. All patients signed informed consent. The study protocol was approved by the local ethics committee and complied with international biomedical ethics requirements.

The design of the study was a prospective, comparative, controlled clinical and immunological observation, the purpose of which was to identify immunological predictors of complicated postoperative course in patients with spondylolisthesis who underwent TPF, as well as to evaluate the effectiveness of personalized immunomodulatory prophylaxis. The work was organized as a step-by-step process: from screening and inclusion of patients according to clear criteria to the construction of a prognostic model, implementation of preventive schemes and subsequent assessment of clinical and immunological outcomes. This approach ensured a comprehensive interpretation of the results and the possibility of practical application of the data obtained.

### **Results and discussions**

The developed model for predicting the risk of complications after TPF in patients with spondylolisthesis allowed stratifying patients by the severity of immunological disorders that have prognostic significance. It was found that at a low risk of complications, moderate deviations in the cellular and proinflammatory link of the immune system prevail: reduced but not critical values of CD4+, moderate increase in IL-6 and MMP-9, as well as borderline values of NLR. Under these conditions, it is possible to achieve a clinically significant effect through preoperative immunocorrection aimed at activating regulatory T cells and reducing background cytokine activity. In contrast, patients with a high immunological risk are characterized by a pronounced CD4+ deficiency, high levels of cytokines (IL-6, TNF- $\alpha$ ), protease activity (MMP-9), and systemic inflammatory overload (increased values of NLR and CD16+/56+). Such an immune profile requires multi-level immunomodulatory support, including both preparation for surgery and postoperative intervention using drugs that act on various links in the immune response - from T-cell to anti-cytokine and histoprotective.

In patients with a low risk of complications after TPF, moderate immunological abnormalities prevailed - moderate decrease in CD4+, borderline increase in IL-6 and MMP-9, normal or slightly increased NLR values. In these conditions, a one-step preoperative regimen was used aimed at stimulating the T-cell link and correcting the innate inflammatory response. It included two drugs: Thymogen at a dose of 100 mcg intramuscularly daily for 5 days as an inducer of differentiation and proliferation of T-helpers; Polyoxidonium at a dose of 6 mg intramuscularly every other day, a total of 3 injections as a module of low-level innate inflammation and a stimulator of phagocytosis.

In patients with a high immunological risk of complications after TPF, the immunological profile included a pronounced CD4+ deficiency, high cytokine activity (IL-6, TNF- $\alpha$ ), a significant increase in MMP-9, and a significant increase in NLR. This justified the need for a two-stage prophylaxis. At the preoperative stage, the same regimen was used as for low risk. In the postoperative period, the following were added: Thymogen - to maintain activation of the T-cell link (another 3 days); Polyoxidonium - an additional course (another 2 injections) to prolong the innate immunomodulatory effect; Cycloferon at a dose of 2 ml intramuscularly every other day  $\times$  5 injections as an interferon-inducing agent aimed at suppressing hypercytokinemia and enhancing the anti-inflammatory background.

Thus, the prophylaxis regimen was strictly personalized and differentiated depending on the severity of the immune imbalance identified before the operation. Such tactics made it possible to influence the key pathogenetic links - immunoregulatory deficiency, cytokine activation, proteolytic aggression and systemic inflammatory response, which formed the basis for the subsequent analysis of the effectiveness of these interventions in the group of patients who received immunoprophylaxis. According to the

accepted risk interpretation scale, in the structure of group 3 (n = 35), 20 patients (57.1%) were classified as low immunological risk. These patients received preoperative immunoprophylaxis aimed at activating the regulatory T-cell link, reducing background cytokine activation and optimizing the inflammatory background before surgery. A combination of Thymogen and Polyoxidonium was used in standard modes.

The remaining 15 patients (42.9%) had a high immunological risk of complications after TFPF, according to the results of the initial assessment. They were prescribed an extended two-stage immunoprophylaxis regimen, including both pre- and postoperative courses. The postoperative phase included continued administration of Thymogen and Polyoxidonium, as well as the addition of Cycloferon to control cytokine hyperreaction. This corresponded to the depth of the identified immunological disorders - severe CD4+ deficiency, IL-6 hyperproduction and high MMP-9 activity. The results of assessing the dynamics of immunological parameters in patients receiving immunomodulatory prophylaxis (group 3) indicate a positive effect of the intervention in both subgroups, with varying degrees of severity. The greatest changes were noted in the high-risk group, which confirms the validity of using an extended prophylaxis regimen in this category of patients.

In the subgroup with low immunological risk of complications after TPFT (n=20), who received only a preoperative course of immunomodulatory therapy, the CD4+ level increased by an average of 4.7 percentage points, which corresponds to a relative increase of 14.6% from the initial value (p<0.01). This indicates the restoration of the regulatory T-cell link under the influence of thymogen-induced stimulation. The CD16+/56+ level decreased by 2.3 percentage points, which corresponds to a decrease of 11.9% from the initial value (p<0.01), indicating a moderate weakening of innate cytotoxic activity. The IL-6 level decreased by 7.2 pg/ml (p<0.01), which reflects the effective suppression of moderate cytokine activation. The MMP-9 content decreased by 15.6% (p <0.01), and the NLR index by 22.9%, indicating a comprehensive normalization of the inflammatory-destructive response. The TNF- $\alpha$  concentration decreased insignificantly (on average from 22.6 $\pm$ 4.5 to 21.4 $\pm$ 4.2 pg/ml), the changes are statistically insignificant (p> 0.05), but a stable downward trend was observed. The IgA level in this subgroup remained within the normal range (up to 2.2 $\pm$ 0.3 g/l).

In the subgroup with a high immunological risk of complications after TPFT (n=15), who received a two-stage immunoprophylaxis regimen including Cycloferon, the changes were more pronounced. The CD4+ level increased by 6.3 percentage points (p<0.001), indicating a deeper correction of T-cell deficiency. The CD16+/56+ level decreased by 3.3 percentage points, which corresponds to a decrease of 15.1% from the baseline level (p<0.001). IL-6 decreased by 10.8 pg/ml (p<0.001), MMP-9 - by 17.6% (p<0.001), and the NLR index - by 35.4% (p<0.001). Such shifts reflect systemic immunotherapeutic modulation of the cytokine, tissue and innate components of inflammation. The TNF- $\alpha$  level decreased from to 27.8 $\pm$ 5.6 pg/ml (p> 0.05), reflecting partial modulation of proinflammatory activity. IgA also tended to decrease (to 2.6 $\pm$ 0.4 g/l), but without statistical significance. These data indicate that the main effects of immunoprophylaxis are realized mainly due to the correction of cellular and cytokine links, while humoral parameters demonstrate greater inertia.

It is important to note that the dynamics of all indicators in the second subgroup was both quantitatively and statistically more pronounced than in low-risk patients, which confirms the feasibility of expanding the immunoprophylaxis regimen in case of profound immunological imbalance. Thus, the immunomodulatory prophylaxis led to reliable positive dynamics of key immunological indicators involved in the pathogenesis of the corresponding disorders in the development of postoperative complications after TFPF in patients with spondylolisthesis. The data obtained confirm its effectiveness, as well as the correctness of preliminary stratification of patients by risk level and the choice of an individualized intervention regimen.

### Conclusion

1. The main effects of immunoprophylaxis are realized mainly due to the correction of cellular and cytokine links, while humoral parameters demonstrate greater inertia
2. The dynamics of all indicators in the second subgroup was both quantitatively and statistically more pronounced than in low-risk patients, which confirms the feasibility of expanding the immunoprophylaxis regimen in case of deep immunological imbalance

3. The immunomodulatory prophylaxis led to reliable positive dynamics of key immunological indicators involved in the pathogenesis of the corresponding disorders in the development of postoperative complications after TPFP in patients with spondylolisthesis

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