IMMUNOCORRECTION OF PATIENTS IN COMPLEX TREATMENT WITH COMBINED INJURIES OF THE FACE BONES

Abstract. The aim of this work is to study the effectiveness of immunomodulatory therapy with the approved drug polyoxidonium in the treatment of patients with concomitant craniofacial injuries.
The study involved 22 patients with concomitant craniofacial injuries as part of complex therapy received polyoxidonium at a dose of 6 mg / m once for 5 days. Clinical and immunological examination was carried out at admission and on the 10th day after the start of treatment. Examination and treatment of patients was carried out at the clinical base of the Department of Maxillofacial Surgery of the Samarkand State Medical Institute in the specialized department of maxillofacial surgery of the Samarkand City Medical Association. The patients were divided into 2 groups:

1-group of 10 patients with concomitant injuries of the lower face zone.
2-group of 12 patients with concomitant injuries of the midface.

The control group consisted of the results of examination of 11 healthy individuals of the same age. It has been proven that in patients with combined injuries of the bones of the facial skeleton from the midface zone, the use of polyoxidonium gives a pronounced immuno-corrective effect at the level of the cellular link of immunity. In the dynamics of complex treatment, positive dynamics were noted in the indices of the content of CD3, CD4, CD16-lymphocytes normalized and were statistically significant in patients with a low baseline level.

**Keywords:** combined injuries of the bones of the facial skeleton, immunity, immunosuppression, immunocorrection, polyoxidonium.

**Relevance.** Combined injury to the bones of the facial skeleton is a triggering factor in the violation of the homeostasis indicators of the body. After an injury, a traumatic illness develops in the body, which is accompanied by the development of inflammatory processes, immune imbalance, and a violation of the secretory and humoral factors of the body’s immune response. Today it has been proven that up to 100% of combined trauma is accompanied by brain damage. The severity of immunological disorders depends on the components and severity of the injury, profound dysfunctions of vital organs. The severity of the general condition of patients depends on the area of damage with combined injuries of the bones of the facial skeleton. In the last decade, there has been a clear tendency to an increase in injuries, especially associated craniofacial injuries. So, according to various authors, the frequency of combined craniofacial injuries ranges from 2.9% to 42.6% [2.9]. Despite the significant progress, the treatment of patients with injuries of the bones of the craniofacial skeleton and the prevention of complications is a difficult and far from resolved problem of modern maxillofacial surgery. The severity is due, on the
one hand, to the problem of the quality and rate of formation of bone regenerate, suffering as a result of injury, and on the other hand, traumatic complications, among which the most important in terms of frequency and severity are complications of a purulent-inflammatory nature, reaching 30% [6,7,9]. The immune system occupies a certain place in the development of bone tissue regeneration and prevention of pyoinflammatory complications [5].

In this regard, it is of great importance to develop new approaches to optimize the treatment of patients with trauma to the craniofacial skeleton, one of which is the inclusion of immunomodulatory drugs in the complex therapy regimens.

Combined injury to the bones of the facial skeleton is a triggering factor for disorders of the immune system. From the beginning, the adaptive mechanisms of cellular immunity are launched. The first manifestation of the body’s response is the reaction of natural factors of immunity, phagocytic activity of neutrophils, the study of the imbalance of pro and anti-inflammatory factors of immune defense is of great prognostic value.

Combined injuries of the bones of the facial skeleton of the middle zone of the face and stress have a more pronounced immunosuppressive effect on the dynamics of the post-traumatic period than in combined injuries of the bones of the facial skeleton of the lower zone of the face. In the post-traumatic period, there is a system of self-regulation of the balance of pro- and anti-inflammatory cytokines. The content of cytokines can be influenced by various complications in the post-traumatic period. For example, an increase in the concentration of IL-6 and a decrease in IL-10 in the blood can serve as a diagnostic sign of pathological changes in the patient’s body.

Analysis of the dynamics of the study of immune parameters with combined injuries of the bones of the facial skeleton from the midface showed that in the dynamics of treatment there is a deep suppression of both cellular and humoral immunity, this is confirmed by an increase in the number of pro-inflammatory and decrease in anti-inflammatory cytokines. Therefore, these changes require the use of immunocorrection in these patients in order to prevent post-traumatic
inflammatory complications. For this purpose, we used polyoxidonium in this group of patients.

It seems promising to use an immunomodulator - polyoxidonium (azoxymer bromide) - an N-oxidized derivative of polyethyleneepiperazine, which has a wide range of pharmacological effects on the body: immunomodulating, detoxifying, antioxidant and membrane-protective effects. The immunomodulatory effect is to increase the ability of neutrophils to absorb and kill absorbed S. aureus; increased cytotoxic activity of NK cells; activation of resident macrophages of the reticuloendothelial system, which leads to a more rapid elimination of foreign particles from the body; increasing the body’s natural resistance to experimental bacterial and viral infections; enhancement of antibody production to T-dependent and T-independent antigens of both animal and bacterial origin. The detoxifying properties of polyoxidonium are associated with its high molecular weight and the presence on the surface of the molecule of a large number of different active groups, therefore it actively adsorbs both soluble toxic substances and microparticles circulating in the blood. The antioxidant properties of polyoxidonium are manifested in the interception of reactive oxygen species (superoxide anion, hydrogen peroxide, hydroxyl radical) in an aqueous medium and in a decrease in the concentration of catalytically active ferrous iron, which leads to suppression of lipid peroxidation [1,7,9].

The aim of this study was to study the effectiveness of immunomodulatory therapy with the approved drug polyoxidonium in the treatment of patients with concomitant craniofacial injuries.

Material and methods. In accordance with the intended purpose of the study, we carried out a comprehensive immunological examination of patients with concomitant craniofacial injuries in the dynamics of treatment with the use of a drug approved for use in healthcare practice - polyoxidonium. 22 patients with concomitant craniofacial injuries received polyoxidonium at a dose of 6 mg / m once for 5 days as part of complex therapy. Clinical and immunological examination was carried out at admission and on the 10th day after the start of treatment. Examination
and treatment of patients was carried out at the clinical base of the Department of Maxillofacial Surgery of the Samarkand State Medical Institute in the specialized department of maxillofacial surgery of the Samarkand City Medical Association. The patients were divided into 2 groups:

1-group of 10 patients with concomitant injuries of the lower face zone underwent traditional methods of treatment.

2- group of 12 patients with concomitant injuries of the midface zone in complex treatment used the drug Polyoxidonium.

Clinical studies were carried out according to the standard scheme and included a survey of patients, collection of an anamnesis of the disease, anamnesis of life, physical research methods (examination, palpation, percussion), laboratory and instrumental additional research methods (general blood analysis, urine, if necessary, a biochemical blood test, X-ray examination of the bones of the facial skeleton and skull), as well as consultation of specialists (neurosurgeon, otorhinolaryngologist, ophthalmologist, traumatologist, anesthesiologist). Immunological research methods included: immunophenotyping of cells (CD3 +, CD4 +, CD8 +, CD16 +, CD19 + lymphocytes) using monoclonal antibodies, the concentration of immunoglobulins of class A, M and G in the blood serum was performed by enzyme immunoassay.

Statistical processing of the results was carried out according to programs developed in the EXCEL package using a library of statistical functions with the calculation of the arithmetic mean (M), the error of the arithmetic mean (m), Student’s criterion (t), the probability of error (p).

**Research results.** As a result of the treatment, there was no positive change in the cellular immunity in patients of the 1st group, with the exception of CD8, CD16 - lymphocytes. The revealed changes in the cellular link of immunity in patients with concomitant injuries of the bones of the facial skeleton from the lower face zone have a transient character.

The transient nature of changes in cellular immunity is confirmed by the immunosuppression of humoral immunity. The study of indices of humoral immunity factors on the 1-3rd, 7th, 14th, and 21st days from the moment of injury showed that
the concentration of humoral factors (IgA, IgM, IgG) in patients was significantly lower than data from the control group only from day 7 (P <0.001) and remained low both on the 14th and 21st days in the dynamics of treatment (P <0.001).

Analysis of the dynamics of the study of immune parameters with combined injuries of the bones of the facial skeleton from the midface showed that in the dynamics of treatment there is a deep suppression of both cellular and humoral immunity, this is confirmed by an increase in the number of proinflammatory and decrease in anti-inflammatory cytokines. Therefore, these changes require the use of immunocorrection in these patients in order to prevent post-traumatic inflammatory complications. For this purpose, this group of patients, we used polyoxidonium.

The study of the features of the clinical course of the post-traumatic period in patients with concomitant craniofacial injuries showed that the immunomodulating therapy with polyoxidonium in the complex of treatment has a high clinical and immunological efficiency.

So, when polyoxidonium is included in the treatment regimen, the stabilization of the general condition of patients occurs faster, and a more rapid regression of systemic and local manifestations of the inflammatory post-traumatic reaction is observed. Temperature normalization occurred 2 ± 3 days after the initiation of immunomodulatory therapy in patients versus 5 ± 6 after traditional treatment (p <0.001). The dynamics of a decrease in the severity of the syndrome of general intoxication and the disappearance of its clinical manifestations in the group receiving immunomodulatory therapy with polyoxidonium were clearly traced. The control of general clinical parameters of peripheral blood made it possible to state earlier normalization when polyoxidonium was included in the treatment regimen. It should be noted that in the group of patients receiving immunomodulatory therapy with polyoxidonium, none of the patients developed a pyoinflammatory complication.

In the study of the immune status of patients with concomitant craniofacial injuries, regularities of the immune response were revealed, expressed by a deficiency of both indicators of the T-cell link - CD3 +, CD4 +, CD8 + cells, as well
as the humoral link of immunity - CD19 + with depression of IgA and IgG production with relatively close to normal values the amount of IgM, which was the basis for the development of a method for correcting immunity disorders with the inclusion of polyoxidonium in the scheme of traditional therapy in patients with combined craniofacial injuries. Thus, the inclusion of polyoxidonium in the scheme of traditional therapy allowed the number of cells of the phenotypes CD3 +, CD4 +, CD8 + and CD16 + in patients of the second group, in the peripheral blood reaching the values of practically healthy individuals. Thus, in patients of the second group, an increase in the level of T-lymphocytes was noted (55.1 ± 0.21% versus 47.9 ± 0.41% before treatment, p <0.05) due to an increase in the content of CD4 + lymphocytes (37.4 ± 0, 32% versus 29.6 ± 0.23% before treatment), CD8 + lymphocytes (23.0 ± 0.24% versus 18.1 ± 0.12% before treatment) and CD16 + lymphocytes (17.4 ± 0.31% versus 16.4 ± 0.39% before treatment).

Table 1

Parameters of the cellular link of the immune system in patients with concomitant craniofacial injuries

<table>
<thead>
<tr>
<th>IS indicators</th>
<th>Control group</th>
<th>Initial values</th>
<th>Traditional treatment 1st group</th>
<th>Traditional treatment + Polyoxidonium 2nd group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3*%</td>
<td>56.4±0.57</td>
<td>47.9±0.41*</td>
<td>49.7±1.05</td>
<td>55.1±0.21*</td>
</tr>
<tr>
<td>CD4*%</td>
<td>35.5±0.37</td>
<td>29.6±0.23*</td>
<td>32.7±0.54*</td>
<td>37.4±0.32*</td>
</tr>
<tr>
<td>CD8*%</td>
<td>19.1±0.31</td>
<td>18.1±0.12</td>
<td>18.7±0.84</td>
<td>23.0±0.24*</td>
</tr>
<tr>
<td>CD16*%</td>
<td>18.1±0.74</td>
<td>16.4±0.39*</td>
<td>16.9±0.85</td>
<td>17.4±0.31*</td>
</tr>
</tbody>
</table>

Note: * - p <0.05 in comparison with control; * - p <0.05 in comparison with the indicators before treatment

When studying the dynamics of indicators of the humoral link of immunity against the background of complex therapy with the immunomodulator polyoxidonium, a tendency to normalization of indicators of humoral immunity was revealed: normalization of the level of CD19 + to control values, an increase in the level of IgA, IgM, IgG. Patients of the second group showed an increase in the level of B-lymphocytes to 21.9 ± 0.67% versus 18.1 ± 0.37% before treatment (p <0.05).
Table 2

Indicators of the humoral link of the immune system in patients with concomitant craniofacial injuries

<table>
<thead>
<tr>
<th>IS indicators</th>
<th>Control group</th>
<th>Initial values</th>
<th>Traditional treatment</th>
<th>traditional treatment + Polyoxidonium</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19⁺%</td>
<td>22,1±0,3</td>
<td>18,1±0,37⁺</td>
<td>18,7±0,41</td>
<td>21,9±0,67⁺</td>
</tr>
<tr>
<td>IgA⁺%</td>
<td>188,4±11,5</td>
<td>137,7±7,1⁺</td>
<td>139,7±4,2⁺</td>
<td>161,7±9,91⁺</td>
</tr>
<tr>
<td>IgM⁺%</td>
<td>111,2±4,47</td>
<td>122,3±6,4⁺</td>
<td>118,1±2,1</td>
<td>132,5±8,1⁺</td>
</tr>
<tr>
<td>IgG⁺%</td>
<td>997,7±24,4</td>
<td>901,2±47,8⁺</td>
<td>1004,2±31,7</td>
<td>1061,7±17,4⁺</td>
</tr>
</tbody>
</table>

Note: ⁺ - p <0.05 in comparison with control; * - p <0.05 in comparison with the indicators before treatment

The clinical and immunological data we obtained showed the advantages of including immunomodulatory therapy in the complex of therapeutic measures compared to traditional treatment without the inclusion of an immunomodulator in patients with combined craniofacial injuries and clearly showed that the positive dynamics of changes in immunological parameters in patients directly correlated with the clinical course of the disease.

Conclusion. Thus, in patients with concomitant craniofacial injuries, an immunodeficiency state is noted with the involvement of both the cellular link of immunity, manifested by a decrease in the level of T-lymphocytes, T-helpers, NK-cells, and B-lymphocytes with depression of immunoglobulin production. The use of polyoxidonium immunomodulator in complex therapy in patients with combined craniofacial injuries made it possible to improve the condition of patients in a shorter time and prevent the development of pyoinflammatory complications due to the positive dynamics of indicators of cellular and humoral immunity.

References:
7. Ibragimov D.D., Immunotерapiya v kompleksном lechenii bol’nykh s travmami kostey litsa. Sbornik materialov pervoy Bukharskoy mezhdunarodnoy konферentsii studentov – medikov i molodozhi 23-25 may 2019 g. g.Bukhara
11. Taniya S. SH. Lecheniya postradavshikh s tyazheloy sochetannoy travmoy: avtoref. dis...dokt. med.nauk.- SPb.,2015.-54s.