

# Interferon Level as Biomarker in Oral Surgery

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**Abstract:** Introduction: During the oral surgical operation, the traumas cause a number of different local and system alterations to the host. The initial response is characterized by rapid production and release of various endogenous mediators. Objective: In accordance with modern scientific research trends, the following objectives of this work have been formulated: determining the serum levels of IFN- $\alpha$  and IFN- $\gamma$  in the peri-operative period, as well as the correlation between the serum levels of IFN and sex and age, possible traumatic damage, time interval of the intervention and the possible objective clinical complications throughout the post-operative period. Material and method: The research was conducted over forty patients at the Clinic of Oral Surgery at the Faculty of Stomatology who had an indication of oral surgical intervention. According to the type of operation, two groups of twenty patients were formed. Namely, patients diagnosed with impaction and patients who had oral surgical intervention on soft tissue. The serum levels of the IFN- $\alpha$  and IFN- $\gamma$  were registered before the surgical intervention, 24 hours after it, and on the seventh day after it, which enabled the formation of a complete image of the individual immune system activity. The ELISA method and the device Medgenix Dianostics, Belgium were used for determining the concentration of the IFN- $\alpha$  and  $\gamma$ . Results and discussion: Post-operative values of the examined groups showed statistically important increase concerning both groups, only that in the first group of patients, patients with impactions, the increase of post-operative values of the examined parameters is greater. With regard to the differences between the groups, there is a statistically significant difference in the examined parameter IFN- $\alpha$ . The duration of the intervention, its complexity, the degree of surgical trauma, the body temperatures, as well as the local post-operative complication, are more notable in the first group of patients. In addition, our study provided data that show medium strong statistically relevant correlation between the duration of the surgical intervention and the changes in the serum levels of IFN- $\gamma$ . In the group of patients with impaction, the subjects differ only with respect to the number of the osteotomized surfaces which has discrete impact on the analyzed system parameters (weak correlation). The organism manages to keep locally the locally produced mediators (to keep them locally according to Bone). This is a good result of the post-operative course of the examined specimen. There is a medium strong significant negative correlation between the pre-operative values of IFN- $\gamma$  and the manifestation of post-operative trismus. Conclusion: The surgical intervention causes an immune and acute phase response, aseptic inflammatory reaction which universally accompanies all kinds of trauma. The rapid post operative increase of the levels of IFN demonstrated and proved high sensitivity which is a reason for emphasizing their responsibility in the systematic immunological response of the organism and it is suitable indicator of tissue trauma.

**Keywords:** IFN; surgical trauma; immunology; oral surgery; postoperative complications

## 1. Introduction

Interferon is a protein or glycoprotein produced by the human cells. It was discovered by Alick Isaac and Linderman Jean in the year 1957 (1). The name „interferon” (to interfere) originates from his ability to impede viral proliferation. The different forms of interferon are fastest products produced by the organism, and most important in the defense against viruses. They belong to the group of the cytokines (intracellular signaling) and represent the product of the cells in stimulation with viruses or other foreign substance, yet they do not directly inhibit viral replication. Interferons possess immunoregulatory functions, they inhibit B-lymphocyte activation, they activate T cells and increase the destructive ability of NK (natural killer) cells. The division of interferons is executed under the functional characteristics of the protein and by the type of cells which produce that protein. Type 1 interferon is produced by all types of cells stimulated by a viral infection, their primary function is to induce viral resistance into the cells. Type 2 is secreted by the NK cells and T lymphocytes. Their main goal is signaling to the immune system, in order to respond to infectious agents or tumor proliferation.

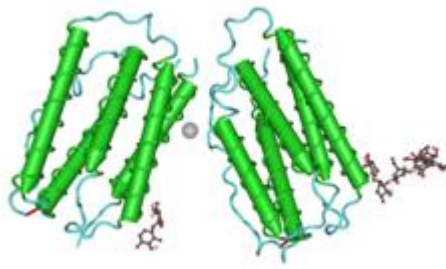
Type 1= IFN  $\alpha$  and  $\beta$  Type 2= IFN- $\gamma$  Type 3= IL-2,29

## IFN- $\alpha$

This interferon was previously known as type 1 interferon. It consists of 166 aminoacids, with 23 variations of aminoacids, some of them glycosylated. It can be formed from different types of cells, as a response to recognition of viral and bacterial nucleic acids. It is heterodimer just the same as IRF-9-interferons regulatory factor (Samuel CE, 2001). It has antiviral effect. IFN- $\alpha$  activates surrounding non-infected cells and virus infected as well. As a result of this intracellular activity the cell proteins are formed, which inhibit the further synthesis of viral particles and dismantle the cover of viral RNA. They increase the number of MHC class I molecules which make the viral infected cells more vulnerable to the attack from T cells. IFN- $\alpha$  then activates NK cells (it possesses antiviral and antitumor - antiproliferative effect).

## IFN- $\beta$

This interferon was previously known as type 1 interferon. It is actually a glycoprotein consisting of 166 aminoacids with 1 variation. It is produced by the viral infected fibroblasts, but also from other cell types. IFN- $\beta$  can connect with the same receptor as IFN- $\alpha$ . (fig.1.)



**Figure 1:** Interferon  $\beta$

### IFN- $\gamma$

This interferon was previously known as type 2 interferon. It is a glycoprotein consisted of 143 aminoacids, present in its active form as heterodimer. It is produced by Th1 (T helper) cells and NK cells, in contact with macrophages that fagocytosed bacteria. IFN- $\gamma$  binds to a specific receptor causing signal transduction through the STAT (signal transduction and transcription) molecule. IFN- $\gamma$  participates in innate and gained immunity. It activates the macrophages at innate immunity and increases their microbicidal function:

- improves the fusion of fagosome with lysosomes
- activates the production of the bacterial nitric oxide and reactive oxygen radicals
- induction of antimicrobial lipids
- hydrolase induction into the macrophages and activation of 25 (OH) vitamin D3 in the 1,25 (OH) 2 vitamin D3, without the production of the inhibitor on the hydroxylases.

IFN- $\gamma$  stimulated macrophages have increased phagocytic ability and increased ability of destroying intracellular pathogens. Considering innate immunity, it does stimulation of the expression of MHC class I and II molecules and costimulatory molecules of the antigens. It promotes the differentiation of naive T cells into Th1 cells, activating the polymorphonuclears and cytotoxic T cells and increases the cytotoxicity of the NK cells. IFN- $\gamma$  secreted by Th1 owns crossed regulatory role in controlling the T function and induces reinclusion to IgG. Actually it can inhibit the activities of Th2 via the induction of the IL-12 production by macrophages. This cytokine possesses roles in a number of different types of immune responses such as deferred type of hypersensitivity, inflammation, production of antibodies and viral infections. IFN- $\gamma$  together with TNF- $\alpha$  are cytokines involved in the management of the macrophages at chronic specific diseases eg. TBC.

Also, this interferon may potentiates antiviral and antitumor effects of IFN- $\alpha$ . It possesses the ability of reducing the creation of scarificated tissue (prevents excessive scarification) through blocking the fibroblasts and inhibing the production of TGF- $\beta$  (molecule of scarification).

## **2. Objective of Labor**

In accordance with modern trends of scientific research that actualize the close relation between surgical traumatic stress factor and its direct impact on the first and direct nonspecific

response, and in order to ensure a peaceful and without complications postoperative flow with fast, complete and functional „recovery“ of the organism, the following objectives of this effort have been formulated:

- 1) To designate the serum concentrations of IFN- $\alpha$  and IFN- $\gamma$  in perioperative period.
- 2) To determine the correlation between the degree of traumatic impairment and the levels of IFN- $\alpha$  and IFN- $\gamma$  in perioperative period, as well as the correlation between time interval of duration of the intervention and the activity of the examined immune parameter.
- 3) To determine the possible influence of gender and age over the immune activity in perioperative period.
- 4) To determine the correlation between examined parameter IFN- $\alpha$  and IFN- $\gamma$  and possible clinical complications in postoperative period.
- 5) To standardize one position for minimization of the traumatic stress, elimination of the cumulative effects of other stressful factors of non-traumatic origin in perioperative period and to determine treatment including immunotherapy in conditions of postoperative immunosuppression.

## **3. Materials and Methods**

In order to accomplish the objectives from the examination, 40 patients were encompassed at the Clinic for Oral Surgery at Faculty of Dentistry in Skopje where oral surgical intervention was indicated after the detailed anamnesis, extraoral and intraoral clinical examination and X-ray analysis. Patients signed written consent for performing the examinations. Also the gender and age of the patients were taken into account. According to the type of the oral surgical intervention two groups with 20 patients were formed, patients with diagnosed impacted teeth and patients with indicated soft tissue surgical intervention. In this study patients who did not have clinical signs of infection or neoplasia before the receipt were included and who were not previously treated for at least three months before the scheduled date for intervention. In the individual formular of the patient were registered both quantitative and qualitative characteristics of performed surgical intervention such as: type of intervention, duration of the intervention, the design complexity as well as the degree of surgical trauma to the periosteum and bone tissue (osteotomy). In subjects every presence or absence of objective postoperative complications, were noted down on the first day of the intervention of general (measurement of body temperature) and local character: presence of postoperative pain, edema, hematoma, postoperative infection, trismus and function forest. The seventh postoperative day "suture ex" is performed and it is without clinical features. Before surgical intervention, 24 hours after it and on the seventh day of the operative intervention in patients were registered the serum levels of IFN- $\alpha$  and IFN- $\gamma$ . Samples of venous blood were taken in quantities of 10 ml. The blood samples were preserved at 2-6°C to 24h. After that, they were centrifuged and kept at a temperature of -20°C until the moment of the laboratory examination.

For the determination of the concentration of cytokines (IL-1, IL-6, TNF- $\alpha$ , IFN $\alpha$  and  $\gamma$ ) the ELISA method was used

and the apparatus Medgenix Diagnostics, Belgium. In determining the level of cytokines we may use various body fluids (urine, serum, plasma, synovial fluids), but as most frequent sample we use plasma and serum. It requires 50-200 µL serum or plasma. The blood is taken by venipuncture and the serum is separated by centrifuging (5 min. 4000 rpm). If it is necessary to preserve the sample for longer than 1 day, it is held at a temperature of -20°C and if it is necessary the samples to be kept longer than a week, then they are kept at -80°C. The concentration of cytokines in the sample is determined by the ELISA method (enzyme linked immunosorbent assay).

Today there are most diverse commercially available kits for determining the concentration of the cytokines that are not always precise e.g. they do not give approximately equal results. Immunologic tests represent an alternative to biological methods and proto-term cytometry. They are simple for derivation and the result is obtained for a few hours. Most often used ELISA method uses two types of antibodies. On microtitration plate with 96 wells are bound immobilized antibodies and they serve to bind the examined matter for themselves. After the first rinsing of the wells, the second antibody is added. The second antibody which is detection antibody owns complex enzyme biotin, HRP (horseradish peroxidase) or alkaline phosphatase. After the second rinsing of the wells, amplified solution Amdex is added that represents a specific multifunctional conjugate and contains molecules of the HRP and streptavidin. This conjugate binds to the cytokine for whom the first-term and second-term antibody are bound. The binding of the antibodies is visible when an enzyme which is bound with the antibody (that detects) and with the amplified solution, reacts with substrate 3,3', 5,5'-tetra-methyl benzidine (TMB). The reaction is stopped by the addition of sulfuric acid. The pigmentation can be read at appropriate wave length with a spectrophotometer or ELISA reader where the intensity of pigmentation is proportional to the examined concentration of the cytokine in the sample. Before start working all chemicals and samples are heat up to a temperature of +20 to 25 °C. The sensitivity of the method is achieved by adjustment of the volume of the sample, the time of incubation, temperature, as well as the use of different buffers and different pH. In our examinations, the values of the interferons are expressed in pg/ml.

Statistical analysis was manufactured by the statistical program STATISTICA 7.

## 4. Results and Discussion

Patients with surgical extraction of the impacted teeth (graph 1).

The group of patients with impactions is made up of 9 (45%) men and 11 (55%) women (Table 1).

**Table 1:** Distribution by gender

| Gender | Number | %    |
|--------|--------|------|
| Male   | 9      | 45.0 |
| Female | 11     | 55.0 |
| Total  | 20     | 100  |

In Table 2. results are shown concerning the changes of IFN-γ and IFN-α.

**Table 2:** Changes in interferon: IFN-γ ; IFN-α.

| Parameter            | N  | Mean | Confidence<br>-95.0% | Confidence<br>+95.0% | Min  | Max  | Std.<br>Dev. |
|----------------------|----|------|----------------------|----------------------|------|------|--------------|
| IFN-γ / before       | 20 | 1.49 | 0.54                 | 2.43                 | 0.47 | 7.65 | 2.02         |
| IFN-γ / 24h<br>after | 20 | 1.96 | 1.01                 | 2.92                 | 0.35 | 7.48 | 2.05         |
| IFN-γ / 7th<br>day   | 20 | 1.46 | 0.58                 | 2.35                 | 0.44 | 7.05 | 1.89         |
| IFN-α /<br>before    | 20 | 1.83 | 1.34                 | 2.32                 | 0.97 | 4.22 | 1.05         |
| IFN-α /24h<br>after  | 20 | 1.74 | 1.24                 | 2.23                 | 0.81 | 4.89 | 1.06         |
| IFN-α / 7th<br>day   | 20 | 1.82 | 1.34                 | 2.31                 | 0.97 | 4.23 | 1.03         |

Table 3.1 and 3.2 expresses the statistical significance of the IFN-γ and IFN-α differences.

**Table 3.1:** Changes in IFN-γ / differences

| Parameter                        | N  | T     | Z    | p-level | p      | Sig. /N. Sig. |
|----------------------------------|----|-------|------|---------|--------|---------------|
| IFN-γ before /<br>IFN-γ 24 hours | 20 | 45.00 | 2.24 | 0.025   | p<0.05 | Sig.          |
| IFN-γ before /<br>IFN-γ 7th day  | 20 | 41.5  | 2.15 | 0.031   | p<0.05 | Sig.          |

**Table 3.2:** Changes in IFN-α / differences

| Parameter                        | N  | T      | Z    | p-level | p      | Sig. /N. Sig. |
|----------------------------------|----|--------|------|---------|--------|---------------|
| IFN-α before /<br>IFN-α 24 hours | 20 | 102.00 | 0.11 | 0.911   | p>0.05 | N.Sig.        |
| IFN-α before /<br>IFN-α 7th day  | 20 | 65.00  | 0.16 | 0.876   | p>0.05 | N.Sig.        |

**Schinkel Christian, Katharina Licht, Siegfried Zedler (2001)** were investigating the behavior of IFN-γ and IFN-α before and after surgical intervention. They stress the fact that IFN-γ represents a key mediator in the regulation of the immune monocyte ability and is a potent pro-inflammatory mediator. It also helps in overcoming the posttraumatic leukocyte and monocyte paralysis. The subject of the study was to define the potential of IFN - γ as a modifier to monocyte activity before and after surgical trauma. The conclusion of the study is that exogen administration on IFN-γ is effective.

**Jesse De Metz, Johannes Romijn, Eric Ender (2004)** referred to show that IFN -γ has no harmful effects on the metabolite and endocrine system in conditions where the immune system of the host is activated. In the study it is established that IFN-γ is ideal cytokine which improves cell-term immune response in surgical patients without any other additional negative effects on active metabolite and endocrine system.

**Joerg-Matthias Brand, Peter Schmucker, Breidhardt Tobias (2001)** stress that the effects of the surgical intervention, surgical stress and anesthesia compromise the optimal function of the immune system. The authors detect increased levels of IFN-γ by surgical intervention.



*Correlation (only statistically significant correlations are given)*

**Correlation: Duration of the intervention/analyzed parameters**

**Table 4:** Duration of the intervention/analyzed parameters

| Parameter                | Pearson / r | p      | Sig. / N.Sig. |
|--------------------------|-------------|--------|---------------|
| IFN- $\gamma$ / before   | 0.53        | p<0.05 | Sig.          |
| IFN- $\gamma$ / 24 hours | 0.19        | p>0.05 | N.Sig.        |
| IFN- $\gamma$ / 7th day  | 0.50        | p<0.05 | Sig.          |
| IFN- $\alpha$ / before   | 0.05        | p>0.05 | N.Sig.        |
| IFN- $\alpha$ / 24 hours | 0.03        | p>0.05 | N.Sig.        |
| IFN- $\alpha$ / 7th day  | 0.06        | p>0.05 | N.Sig.        |

Correlation: Duration of the intervention / Changes in IFN - gamma

The examined relationship between the duration of the intervention and IFN- $\gamma$  (before intervention) for  $r = 0.53$  ( $p < 0.05$ ) is a medium strong and significant, i.e. the increase of the time of intervention is followed by increasing the values of IFN-  $\gamma$  (before).

**Correlation: Degree of surgical trauma/analyzed parameters**

When analyzing the results of the relationship between the degree of surgical trauma and analyzed parameters, no significant relations are registered ( $p < 0.05$ ).

A number of authors are investigating the mechanisms of the tissue impairment, stress-conditioned tissue impairment and the mediators in tissue impairment that bring to the activation of the non-specific and specific immunity. **Watson T (2003)** as well as **Wagner (2003)** revise the four processes that occurs during the damage of the soft tissues: bleeding, inflammation, proliferation and remodeling. In the process of inflammation there are two events as follows: vascular and cellular cascade. After the initial vasoconstriction, vasodilation comes with changes in the caliber of blood vessels, changes in the wall of the blood vessels and their permeability as well as changes in blood flow through them. The reason for these changes in the blood vessels are chemical substances, histamine, prostaglandins, complement cascade, leukotrienes, serotonin (5-HT) and the axon reflexes. In relation to the cellular events during the inflammatory response, the authors stress the early migration of PMN polymorphonuclear neutrophils) as well as (monocytes, lymphocytes, eosinophils, basophils and a small number of red blood cells). The main chemical mediators responsible for chemotaxis are the components of the complement system, the factors released by PMN , peptides from fat cells and damaged tissue, PDGF (platelet derived growth factor) released from the injured platelets, leukotrienes (free of leukocytes, fat cells and macrophages) and lymphokines (free of PMN).

**Sota Omoigui (2002)** pays attention to the existence of complex interactions of inflammatory mediators that are exempt by traumatic tissue impairment and describes the details of different paths of their creation (bradykinin,

phospholipase A2 enzyme, arachidonic acid, substance P, MMP-9 which includes the collagenase and stromelysin).

Another group of authors clearly precize the difference of the effects on the immune system in different types of tissue as well as the quantitative level of the liberation of the mediators during inflammation at different types of tissue (bone tissue contains the larger number of mediators during the tissue impairment than soft tissue).

**Matthias Wichmann, Alfred Ayala (1998)** are investigating the impact of the isolated tissue damages at soft tissues or bone tissues as well as combined tissue damages (soft tissue and bone tissue) on the immune system, and they come to the conclusion that at combined tissue impairments there exist significant depression of cytokine production compared to isolated tissue impairment.

Heating of the bone tissue in oral surgical interventions according to **Sternfeld DS, Ogle CK (1997)** qualitatively change the monocyte-macrophage function even it quantitatively and qualitatively influence the hematopoiesis. These cells produce less acute phase proteins (APPs) C3 and transferrin, but have greater cytotoxicity measured according to the liberation of l-lactate dehydrogenase.

In our study the group of patients with impaction, respondents differ between themselves only with the number of osteotomised surfaces, which seems to give discrete impact on systemic analyzed parameters (weak correlation). When considering locally produced mediators, the organism according to its individual abilities, manages to sustain them locally (to keep them locally). This represents a good outcome in postoperative process in examined sample.

**Correlation: Trismus/analyzed parameters**

**Table 5:** Trismus/analyzed parameters

| Parameter                | Spearman / R | P      | Sig. / N.Sig. |
|--------------------------|--------------|--------|---------------|
| IFN- $\gamma$ / before   | -0.47        | p<0.05 | Sig.          |
| IFN- $\gamma$ / 24 hours | -0.25        | p>0.05 | N.Sig.        |
| IFN- $\alpha$ / before   | -0.09        | p>0.05 | N.Sig.        |
| IFN- $\alpha$ / 24 hours | 0.22         | p>0.05 | N.Sig.        |

**Correlation: Trismus/changes in IFN- $\gamma$**

In **Table 5.** presents the results of the examined relationship between trismus and analyzed parameters. This relationship between the changes of trismus and the value of IFN- $\gamma$  (before intervention) for  $R = -0.47$  ( $p < 0.05$ ) shows a medium strong significant negative correlation, where the values of IFN- $\gamma$  before intervention decrease, and the values of the trismus increase. This data refer to the fact that as much the values of interferon are lower considering the individua (preoperative), that much the probability of the occurrence of trismus increases (due to the local complications: infection, trauma).

**Difference between the groups:**

In **Table 6.** and **Table 7.** the results are presented concerning the differences between the analyzed parameters,

between the groups. Significant differences are registered between the following parameters:

-for  $Z = -2.16$  and  $p < 0.05$ , 24 hours from operational intervention in the group of patients with soft tissue surgery (group 2), the value of IFN- $\alpha$  is significantly higher than in the group of patients with impactions (group 1). Namely, the higher the degree of surgical trauma, the greater is the probability of postoperative decrease of the values of IFN- $\alpha$  e.g. there is a greater probability of immunosuppression, or inadequate response to the organism.

-for  $Z = 5.18$  and  $p < 0.001$ , duration of the intervention in the group of patients with impactions (group 1) is significantly longer than in the group of patients with soft tissue surgery (group 2).

-for  $Z = 4.33$  and  $p < 0.001$ , complexity of the intervention in the group of patients with impactions (group 1) is significantly higher than in the group of patients with soft tissue surgery (group 2).

-for  $Z = -5.41$  and  $p < 0.001$ , the degree of surgical trauma in the group of patients with impactions (group 1) significantly dominates compared to patients with soft tissue surgery (group 2). **That is how much the degree of surgical trauma is higher (soft tissue, periosteum, bone tissue) that much the greater is the probability for reduced response to the organism e.g. immunosuppression.**

-for  $Z = 4.61$  and  $p < 0.001$ , body temperature by intervention in the group of patients with impaction (group 1) is significantly higher than in patients with soft tissue surgery (group 2).

-for  $Z = 4.11$  and  $p < 0.001$ , the pain after the intervention in the group of patients with impaction (group 1) is significantly present than in patients with soft tissue surgery (group 2).

-for  $Z = 3.96$  and  $p < 0.001$ , after the intervention edema was significantly registered in the group of patients with impaction (group 1) than in patients with soft tissue surgery (group 2).

-for  $Z = 3.79$  and  $p < 0.001$  there is a significant difference considering trismus, namely after the intervention trismus is only registered in the group of patients with impaction (group 1), in patients with soft tissue surgery (group 2) is not registered.

-for  $Z = 3.79$  and  $p < 0.001$  there is a significant difference considering the disorder of the function, namely after the intervention, disorder is only registered in the group of patients with impaction (group 1), in patients with soft tissue surgery (group 2) is not registered.

-for  $Z = 2.98$  and  $p < 0.01$  there is a significant difference concerning the presence of regional lymphadenitis, namely after the intervention, the regional lymphadenitis was only registered in the group of patients with impaction (group 1), in patients with soft tissue surgery (group 2) is not registered.

In the other analyzed parameters for  $p > 0.05$ , no significant difference was determined.

**Table 7:** Differences considering the analyzed parameters between the groups.

| Parameter                      | Rank sum / Grupa 1 | Rank sum / Grupa 2 | Z / t        | p-level | p           | Sig. / N. Sig. |
|--------------------------------|--------------------|--------------------|--------------|---------|-------------|----------------|
| IFN- $\gamma$ / before         | 339.50             | 480.50             | -1.91        | 0.057   | $p > 0.05$  | N.Sig.         |
| IFN- $\gamma$ / 24 hours       | 411.00             | 403.00             | 0.19         | 0.849   | $p > 0.05$  | N.Sig.         |
| IFN- $\gamma$ / 7th day        | 347.00             | 473.00             | -1.70        | 0.088   | $p > 0.05$  | N.Sig.         |
| IFN- $\alpha$ / before         | 347.00             | 473.00             | -1.70        | 0.088   | $p > 0.05$  | N.Sig.         |
| IFN- $\alpha$ / 24 hours       | 330.00             | 490.00             | <b>-2.16</b> | 0.030   | $p < 0.05$  | <b>Sig.</b>    |
| IFN- $\alpha$ / 7th day        | 342.00             | 478.00             | -1.84        | 0.066   | $p > 0.05$  | N.Sig.         |
| Duration of the intervention   | 601.50             | 218.50             | <b>5.18</b>  | 0.0000  | $p < 0.001$ | <b>Sig.</b>    |
| Complexity of the intervention | 570.00             | 250.00             | <b>4.33</b>  | 0.0000  | $p < 0.001$ | <b>Sig.</b>    |
| Degree of surgical trauma      | 210.00             | 610.00             | <b>-5.41</b> | 0.0000  | $p < 0.001$ | <b>Sig.</b>    |
| Body temperature               | 580.50             | 239.50             | <b>4.61</b>  | 0.0000  | $p < 0.001$ | <b>Sig.</b>    |

**Table 8:** Differences concerning local complications

| Parameter              | Rank sum / Grupa 1 | Rank sum / Grupa 2 | Z / t | p-level | p           | Sig. / N. Sig. |
|------------------------|--------------------|--------------------|-------|---------|-------------|----------------|
| Pain                   | 562.00             | 258.00             | 4.11  | 0.0000  | $p < 0.001$ | <b>Sig.</b>    |
| Edema                  | 556.50             | 263.50             | 3.96  | 0.0001  | $p < 0.001$ | <b>Sig.</b>    |
| Hematoma               | 400.00             | 420.00             | -0.27 | 0.787   | $p > 0.05$  | N.Sig.         |
| Trismus                | 550.00             | 270.00             | 3.79  | 0.0002  | $p < 0.001$ | <b>Sig.</b>    |
| Disorder function      | 550.00             | 270.00             | 3.79  | 0.0002  | $p < 0.001$ | <b>Sig.</b>    |
| Regional lymphadenitis | 520.00             | 300.00             | 2.98  | 0.003   | $p < 0.01$  | <b>Sig.</b>    |
| Infection              | 410.00             | 410.00             | 0.00  | 1.00    | $p > 0.05$  | N.Sig.         |

## 5. Conclusions

- Surgical intervention causes immune and acute phase response, the aseptic inflammatory reaction, which universally accompanies all types of trauma.
- Rapid increase in the levels of interferons postoperatively, demonstrate and prove high sensitivity. From the obtained results of the examined parameter, we concluded that it is justified to use the diagnostic tests for determining the levels of interferons as landmark for the degree of postoperative inflammation and they represent effective prognostic tool. Knowledge of the interferon levels may give us insights to intracellular changes (intracellular milieu) as well as the directions in further treatment.
- According to our examination and according to a number of studies the thesis is confirmed that the greater is the degree of surgical trauma (soft tissue, periosteum, bone tissue) the greater is the probability for inadequate respond to the organism e.g. immunosuppression. In the group of patients with impaction, respondents differ between themselves only with the number of osteotomised surfaces which seems to give discrete impact on systemic analyzed parameters (weak correlation). According to its individual abilities, the organism manages to sustain the locally produced mediators (to keep them locally). This represents a good outcome in postoperative process at examined sample.

- There is a medium strong significant negative correlation between the values of IFN- $\gamma$  preoperative and the manifestation of the postoperative trismus. This data refer to the fact that as lower the values of the interferon (preoperative), the higher is the probability of the occurrence of trismus as local postoperative complication.
  - The minimum pain, faster „recovery" and shorter hospital process are the benefits of minimally invasive surgery. Here comes the recommendation for the selection of the methods of the modern minimally invasive surgery before the methods of conventional surgery, in all those cases where it is indicated.
  - In accordance with the previously reported conclusions we can see the importance of minimizing the traumatic stress underway to oralsurgical interventions, by favoring non-traumatic approach, minimizing the pressure and vibrations during the intervention, reducing the temperature which increases during osteotomy (using systems with continuous internal and external cooling, reducing the number of spins in minutes of the instruments), using burs from high quality materials and with sufficient rigor.
  - With equal importance is the elimination of stress factors of non-traumatic origin through the use of premedication (anxiolytics, analgesics) as well as psychological techniques and strategies for the reduction of stress (stress reduction strategies).
  - It is recommended antibiotic and anti-inflammatory prophylaxis in a complicated, long-lasting and volumetric interventions.
  - Steroidal and non-steroidal anti-inflammatory agents, cytokines IL-4, IL-10, IL-13 reduce the production of the proinflammatory cytokine. The most modern administration of these agents may be effective in the attenuation of the post traumatic and postoperative hyperinflammation.
  - Modern scientific trends favorize new immunomodulatory strategies: immune diets to increase immunity, the use of hypertonic solutions for resuscitation and reduction of the incidence in septic shock .
  - Injury, trauma and the loss of blood ( with hemorrhage ) may produce suppression to the celular immunity and increased opportunity for the development of consecutive sepsis and infection of the wound. The use of various immunomodulatory agents (e.g. dilitazem, chloroquine, ibuprofen, IFN- $\gamma$ , prolactin, metclopramide and flutamide) helps in normalizing the immune altered response during the trauma or hemorrhage at experimental studies. This contributes to the development of new therapeutic concepts at immunosuppression and reduction of mortality in consecutive sepsis in patients.
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