

## ТЕОРЕТИЧНА І ЕКСПЕРИМЕНТАЛЬНА МЕДИЦИНА

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### DYNAMIC STUDY OF CONCENTRATIONS OF INFLAMMATORY AND ANTI-INFLAMMATORY INTERLEUKINS IN PATIENTS WITH NECK INJURIES

The cytokine status was studied in 64 patients with neck injuries and damage to internal structures. Severe trauma causes damage to the protective barriers of the organism and activates immunological reaction. Among substances secreted during this process pro-inflammatory cytokines are of high importance. It is shown, that monitoring of cytokine status (IL-6, IL-8, IL-10, TNF $\alpha$ ) in the acute period of trauma had been having important clinical, prognostic and diagnostic values. A dynamic study of the concentrations of pro-inflammatory and anti-inflammatory interleukins during the first ten days in patients, together with clinical data, made it possible to change the routine treatment tactics and optimize the terms and scope of surgical care. The TNF $\alpha$  is a reliable indicator of a developing infectious complication and takes a chance to change antibacterial or anti-inflammatory therapy and improve effects of therapy.

**Keywords:** neck injury, kinin-kallikrein system, cytokine status, surgical treatment.

#### Introduction

Over the past decade, there has been a steady increase in injuries as the social conditions of life and have changed: urbanization, an increase in the number of vehicles, non-compliance with safety standards at work [1, 2].

Out of the total number of injured, outpatient trauma increased by 5,9 %, while the number of patients requiring hospitalization increased by 64,0 % [3, 4].

It is statistically found that 54,0 % of victims of car accidents have injuries to the head and neck. The combination of neck injuries with injuries of other anatomical regions were distributed as follows: 19,0 % were with chest, 20,0 % were with abdomen, 7,0 % were with spine and up to 14,0 % were with combinations with pelvic injuries [5].

The presence of hematomas, displacement of bone fragments, hemorrhages, subcutaneous emphysema, nasal and oral bleeding and pain syndrome – all these factors complicate the assessment of the functional state of cranial nerves and contribute to the growth of edema brain [6, 7].

Mechanical damage as a source of cellular proteases, blood loss and increasing hypoxia it activates the components of the body's non-specific resistance: coagulation processes, fibrinolysis, activation of the kinin-kallikrein system [2, 4]. At the same time, neutrophils, monocytes, macrophages, mast cells are activated, which is accompanied by the release of inflammatory mediators and contribute to the subsequent transition of inflammation to its generalized form. This form is a systemic inflammatory response syndrome [8].

According to modern immunologists, who are analyzing the cytokine status of patients with injuries in the early stages after receiving it, levels of  $\text{TNF}\alpha$ , IL-1 $\beta$  increase in 1 hour after injury in the systemic circulation. After 12 hours the injury were noted the increase in the level in the systemic circulation: IL-6, IL-8, IL-10. However, in severe and complicated injuries, the levels of pro-inflammatory cytokines begin to prevail over anti-inflammatory ones and this imbalance deepens due to the inhibition of the next stage in the synthesis of cytokines [9, 10].

It is quite logical that operations and anesthesia are enhanced immunosuppression by performed according to vital indications for neck injuries with damage to internal structures [1, 8, 11]. The most important function of the cytokine cascade in the immune hierarchical system is to do a coordinated harmonious action of the immune, endocrine and nervous systems in response to stress [2, 8].

That is why, the dynamics of the cytokine profile in patients with severe neck injuries most reliably reflects the general biological response of the body to injury. In our study, we paid special attention to monitoring the cytokine status, its pro-inflammatory and inflammatory units: IL-6, IL-8, IL-10 and  $\text{TNF}\alpha$  as the most significant interleukins, which reflect the reaction of the immune system to neck injuries with damage to internal structures.

Aim of research is study of changes in the cytokine profile in patients with severe trauma for subsequent analysis and development of therapeutic tactics.

#### **Materials and methods**

The study was conducted in SI «V.T. Zaitsev Institute of General and Emergency Surgery of NAMS of Ukraine» (from 2016 to 2019 years) and we were analyzed cytokine status indicators in 64 patients with neck injuries and damage to internal structures.

Patients were divided into the main (I) and comparison (II) groups. The main group of patients includes 31 patients treated using an integrated surgical approach and modified interventions. The II group is represented by 33 patients, who were operated in the traditional way over the same period of time. The average age of the patients was (34,3 $\pm$ 8,4) years, at the age under 40 years old was 77,4 %. All groups were representative by gender, age and nature of the pathology.

The main access for neck in patients of I group with injuries and damage to internal structures is mini-colotomy with using a ring-shaped retractor. In the I group, for all patients, regardless of the time after the injury, the defect of the pharynx and esophagus wall was sutured from the condition of the surrounding local tissues of the neck. The suture line of the esophagus was strengthened with a portion of the sterno-cleido-mastoid muscle. In the II group, sutures on the defect of the pharynx and esophagus were applied only in the early stages after perforation (up to 6 hours), and with a later detection of damage and in the presence of signs of inflammation, the cervical esophagus defect was just drained. We were not doing a primary resection of a perforated and pathologically altered esophagus.

All surgical interventions ended up with drainage of the paraesophageal tissue. Active aspiration Redon's drainage was used in the main group. A passive drainage (polyvinyl chloride tubes) and their combination with tampons were used in the comparison group. A gastrostomy or nasogastric tube was installed in order to turn off the damaged esophagus from the food passage and ensure enteral nutrition. In the patients (I group) with penetrating wounds of the pharynx we were fixing nasogastric tube (material from polyvinyl chloride), which provided functional rest, good nutrition and did not interfere with the healing of damage to the esophagus. We formed the gastrostoma in patients with external wounds (the comparison group) in a third of them. Surgical treatment of penetrating wounds was combined with adequate general therapy (antibacterial, infusion, blood transfusion).

Diagnosis of interleukin titers was carried out using reagent kits for enzyme-linked immuno-sorbent assay (ELISA): «Vector-Best» on the device «Biorat». Specific reagents of the kits were monoclonal antibodies to IL, adsorbed on the surface of wells, a collapsible polystyrene plate, conjugate of polyclonal antibodies to IL with biotin and calibration samples containing IL. At the first stage of the analysis, the test and control samples were incubated in wells with immobilized antibodies.

#### **Results and discussion**

The dynamics of cytokines in patients with neck injuries with damage to internal structures is presented in *table*.

In a dynamic study of IL, we revealed a completely natural increase in IL-6 level on the

*The dynamics of the cytokines concentration in patients of the studied groups, pg/ml*

Group	Study period, days	IL-6	IL-8	IL-10	TNF $\alpha$
	Normal rate	0–10	0–10	0–31	0–6
I	1 <sup>st</sup>	17,38 $\pm$ 1,60	38,59 $\pm$ 8,08	3,44 $\pm$ 0,23	2,25 $\pm$ 0,45
	3 <sup>rd</sup>	6,94 $\pm$ 0,85	28,73 $\pm$ 8,13	4,36 $\pm$ 0,99	4,29 $\pm$ 2,01
	7 <sup>th</sup>	5,43 $\pm$ 0,55	38,56 $\pm$ 5,95	5,90 $\pm$ 1,39	6,54 $\pm$ 2,60
	10 <sup>th</sup>	4,75 $\pm$ 0,56	34,78 $\pm$ 5,62	5,67 $\pm$ 1,51	5,81 $\pm$ 2,81
II	1 <sup>st</sup>	20,62 $\pm$ 2,14	30,34 $\pm$ 10,60	5,98 $\pm$ 1,39	2,72 $\pm$ 0,26
	3 <sup>rd</sup>	10,30 $\pm$ 1,34	20,22 $\pm$ 9,72	7,19 $\pm$ 1,07	4,86 $\pm$ 0,71
	7 <sup>th</sup>	7,89 $\pm$ 0,98	32,72 $\pm$ 8,60	15,83 $\pm$ 2,14	7,16 $\pm$ 1,22
	10 <sup>th</sup>	6,64 $\pm$ 0,86	19,77 $\pm$ 4,92	14,59 $\pm$ 2,47	7,61 $\pm$ 1,57

Note.  $p \leq 0,05$  when comparing the indicators in patients of the main and comparison groups.

1<sup>st</sup> day after the injury in patients of both groups, which corresponds to the law of general biological stress response, followed by a decrease in this indicator by the 3<sup>rd</sup> day. The highest values of IL-8 concentration were represented in patients with multiple injuries of the internal structures of the neck.

The analyzing the dynamics of the cytokine status in all groups, there was a significant increase of IL-6 level in circulating blood on the 1<sup>st</sup> day with normalization of this index to the 3<sup>rd</sup> day in 87,0 % of cases. In 13,0 % of cases, normalization of IL-6 values by 5–7 days did not occur (values exceeding 10 pg/ml), which we regarded as an unfavorable factor, which is an indicator of the development of possible infectious complications.

In a retrospective analysis of a long stage of high titers of IL-6 with clinical cases of inflammatory complications, the correlation reached 90,0 %. The most clinically significant was the study of the dynamics changes in IL-8 values. At the first stage (the first three days), the dynamics of IL-8 concentrations is similar to IL-6 changes. In our study, we saw a rapid increase in IL-8 during the first twenty four hours after injury with maximum IL-8 values (12 hours after injury), followed by normalization of the values within 3 days, which was typical for the uncomplicated course of neck injuries. In a situation where high titers of IL-8 persisted for more than 4–5 days, which has a pro-inflammatory character (was in 4 patients in each group with a subsequent adverse clinical outcome). Therefore, in these cases, we considered IL-8 level as an unfavorable indicator in the development of infectious complications.

A IL-10 blood concentration in our study was the main indicator of the development of inflammatory complications. According to modern

domestic and foreign researchers, only in severe trauma does a significant increase in level of IL-10 occur. In our study, only in 2 cases of each group the maximum permissible values of IL-10 were presented on day 10 (more than 31 pg/ml), which was observed in patients with long-term high numbers of IL-8. No less important diagnostic value in the study was study of the TNF $\alpha$  dynamics. In the uncomplicated course of a traumatic disease, there are no significant changes in the concentration of TNF $\alpha$ . We observed an increase in the concentration of TNF $\alpha$  from 4–5 days in 6 patients (all groups) with maximum numbers of TNF $\alpha$  by 10 days, the values of which exceeded the normal by 3–4 times (0–6 pg/ml).

According to published data, an increase in the concentration of TNF $\alpha$  after 4 days from the moment of injury is an unfavorable prognostic indicator and should alert doctors to change (strengthen) therapy and to start the search of wound infection in the form of a local, visceral or generalized form. Surgical interventions with progressive numbers of TNF $\alpha$  have the highest risk of developing complications.

In our study, the increase in TNF $\alpha$  titers from 4 days and performing operations lied to the development of early and late complications (suppuration of soft tissues was observed in 6,0 %, mediastinitis was observed in 9,0 %, inflammatory changes from anastomoses was observed in 12,0 %). In 7 patients of the main group, with an increase in the concentration of TNF $\alpha$  from 3–4 days, surgical treatment was delayed, antibacterial and anti-inflammatory therapy was carried out, which made it possible to exclude the development of complications in the short and long periods. In the main group, local inflammatory signs in the wound area subsided earlier and were less pronounced than signs in the comparison group.

On the 7<sup>th</sup> day after surgery, the width of the hypoechoic zone (ultrasound) in the area of postoperative wounds in the main group of patients was 1,6 times less than the width in the comparison group. This indicates that in the comparison group a wider zone of tissues near the edges of the wound is involved in the inflammation process than in patients of the main group. On the 14<sup>th</sup> day, the decrease in the width of the hypoechoic zone of the postoperative wound area in the main group occurred by 35,2 % and in the comparison group occurred by 18,2 % compared to the 7<sup>th</sup> day. By the end of the 3<sup>rd</sup> week of studies, the width of the hypoechoic zones in the main group and the comparison group were (3,1±0,3) cm and (6,1±0,5) cm. By the end of 4 weeks the indicators were (2,3±0,2) cm and (4,2±0,6) cm.

The average value of the width of the hypoechoic zone in the main group remained less than this index in the comparison group. A comparative analysis shows that the width of the hypoechoic zone of the postoperative scar in patients of the main group was half that of patients in the comparison group, which indicates the subsidence of local signs of inflammation in the wound area, the transition of the inflammation process to the phase of regeneration and formation of connective tissue scar. Conducting in the early stages of a less traumatic modification of the operation of colotomy with suturing the wounds of the larynx and trachea, pharynx and

esophagus will improve the functions of respiration, swallowing, voice formation and achieve the best cosmetic effect and prevent rough scarring in the treatment of patients with damage to the internal structures of the neck.

### Conclusions

Monitoring of cytokine status in patients with damage to the internal structures of the neck in the acute period has important clinical, prognostic and diagnostic value. A significant increase in the concentrations of the pro-inflammatory cytokines IL-6, IL-8 on the first day of a traumatic disease show us an adequate response of the immune system to mechanical trauma with subsequent restoration of balance and normalization of indicators by 3–4 days. We observed the development of an imbalance in the immune response in 6 (9,0 %) cases, which was expressed in high concentrations of IL-10 and TNF $\alpha$  with the clinical development of infectious complications in all cases. The role of monitoring pro-inflammatory and inflammatory cytokines is extremely important for clinicians. In the laboratory stage of a developing (predicted) complication, the diagnosis of a progressive increase in IL-10 and TNF $\alpha$  levels are a reliable indicator of a developing infectious complication from 4 days and a guide to the actions of the clinician: changing antibacterial or anti-inflammatory therapy, surgical treatment after normalize indicators.

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**М.Ю. Сизий**

#### **ДИНАМИЧЕСКОЕ ИССЛЕДОВАНИЕ КОНЦЕНТРАЦИЙ ВОСПАЛИТЕЛЬНЫХ И ПРОТИВО-ВОСПАЛИТЕЛЬНЫХ ИНТЕРЛЕЙКИНОВ У ПАЦИЕНТОВ С ТРАВМАМИ ШЕИ**

Исследован цитокиновый статус у 64 пациентов с повреждениями шеи и повреждением ее внутренних структур. Показано, что мониторинг цитокинового статуса (IL-6, IL-8, IL-10, TNF $\alpha$ ) в остром периоде травмы имеет важное клиническое, прогностическое и диагностическое значение. Благодаря динамическому исследованию концентраций провоспалительных и противовоспалительных интерлейкинов в течение первых десяти дней у пациентов вместе с клиническими данными была изменена тактика рутинного лечения и оптимизированы сроки и объем хирургического лечения.

**Ключевые слова:** травма шеи, кинин-калликреиновая система, цитокиновый статус, хирургическое лечение.

**М.Ю. Сизий**

#### **ДИНАМІЧНЕ ДОСЛІДЖЕННЯ КОНЦЕНТРАЦІЙ ЗАПАЛЬНИХ І ПРОТИЗАПАЛЬНИХ ІНТЕРЛЕЙКІНІВ У ПАЦІЄНТІВ ІЗ ТРАВМАМИ ШІЇ**

Досліджено цитокиновий статус у 64 пацієнтів з ушкодженнями шії і пошкодженням її внутрішніх структур. Тяжка травма завдає шкоди захисним бар'єрам організму й активізує імунологічну реакцію. Із речовин, що виділяються в ході цього процесу, прозапальні цитокіни відіграють важливу роль. Показано, що моніторинг цитокинового статусу (IL-6, IL-8, IL-10, TNF $\alpha$ ) у гострому періоді травми має важливе клінічне, прогностичне та діагностичне значення. Завдяки динамічному дослідженню концентрацій прозапальних і протизапальних інтерлейкінів протягом перших десяти днів у пацієнтів разом із клінічними даними було змінено тактику рутинного лікування та оптимізовано терміни й обсяг хірургічного лікування. Фактор некрозу пухлин- $\alpha$  є надійним індикатором розвитку інфекційного ускладнення, що дозволяє змінити антибактеріальну, протизапальну терапію та поліпшити її результати.

**Ключові слова:** травма шії, кінін-калікрейнова система, цитокиновий статус, хірургічне лікування.

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