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DYNAMICS OF CHANGES OF C-REACTIVE PROTEIN IN THE SERUM CONTENT IN PATIENTS WITH PHLEGMONS OF THE JAWS AND FACIAL LOCALIZATION AT DIFFERENT TERMS OF THE DRUG

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C-reactive protein, a highly conserved pentameric protein from the pentraxin family, is a classic acute phase protein and is not only a marker, but also a pro-inflammatory pathogenic factor in inflammatory reactions. C-reactive protein is part of the innate immune response and can influence the immune response via opsonization of microorganisms as well as via activation of the complement cascade. In poly-traumatized and septic patients, the uncontrolled activation of the complement system can lead to an excessive inflammatory reaction with increasing end-organ damage, including via the activation of the complement factor C5. C-reactive protein was the first identified member of the group of so-called "acute phase proteins". Virtually all acute phase proteins are normal components of blood plasma that have different physicochemical properties. A characteristic feature that combines these proteins into one group is an increase in their concentration in the blood in response to a number of stimuli (infectious diseases, inflammation, trauma, necrosis, tumor growth), which lead to tissue damage. It is proved that the increase in the level of acute phase protein in the blood is due to increased synthesis by the liver with the development of the so-called systemic inflammatory response syndrome.

Key words: phlegmone, maxilo-facial location, inflammation, protein, chronotype.

К.П. Локес, В.О. Личман, Д.В. Стебловський, В.В. Бондаренко, Д.С. Аветіков ДИНАМІКА ЗМІН ВМІСТУ С-РЕАКТИВНОГО БІЛКУ В СИРОВАТЦІ КРОВІ ПАЦІЄНТІВ ІЗ ФЛЕГМОНАМИ ЩЕЛЕПНО-ЛИЦЕВОЇ ЛОКАЛІЗАЦІЇ НА РІЗНІ ТЕРМІНИ ЛІКУВАННЯ

С-реактивний білок, висококонсервованій пентамерний білок з сімейства пентраксинів, є класичним білком гострої фази і є не тільки маркером, але і провоспалительним патогенним фактором запальних реакцій. С-реактивний білок є частиною вродженої імунної відповіді і може впливати на імунну відповідь шляхом опсонізації мікроорганізмів, а також шляхом активації каскаду комплементу. У політравмованих та септичних пацієнтів неконтрольована активація системи комплементу може призвести до надмірної запальної реакції зі збільшенням пошкодження кінцевих органів, у тому числі через активацію фактора комплементу C5. С-реактивний білок був першим ідентифікованим членом групи так званих «білків гострої фази». Практично всі білки гострої фази є нормальними компонентами плазми крові, які мають різні фізико-хімічні властивості. Характерною особливістю, що об'єднує ці білки в одну групу, є збільшення їх концентрації в крові у відповідь на низку подразників (інфекційні захворювання, запалення, травми, некроз, зростання пухлини), які призводять до пошкодження тканин. Доведено, що підвищення рівня білка гострої фази в крові обумовлено посиленням синтезу печінкою з розвитком так званого синдрому системної запальної реакції.

Ключові слова: флегмона, щелепно-лицева локалізація, запалення, білок, хронотип.

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Phlegmon-purulent diffuse inflammation of the tissue located under the skin, mucous membranes, between muscles and fascia [2, 6, 9]. In most cases, patients are caused by poor or untreated periodontal teeth, retained teeth and careless behavior of patients, as well as the cause of inflammatory processes, namely odontogenic phlegmon of the maxillofacial localization is a causal tooth. That is why the level of C-reactive protein in the human body increases. C-reactive protein (CRP) is an acute inflammatory protein that increases up to 1000 times at sites of infection or inflammation [3-4].

To define the individual features of the organization of circadian rhythms, the term chronotype" was proposed, which is becoming increasingly popular in research in the field of medicine [5]. According to the analysis of literature data, biological rhythm affects not only the mental state [10], obesity, but the human condition as a whole. Biological rhythms are a manifestation of the fundamental properties of the organic world, provide the ability of man to adapt and survive in the environment [1, 7]. In this aspect, of particular interest is the functioning of the organism taking into account its individual characteristics in terms of organization of biorhythmic processes[8-12].

The purpose of the study was to examine the dynamics of laboratory blood markers containing the C-reactive protein in the use of cryopreserved placenta in patients with phlegmones of maxillofacial localization and different types of chronotype.

Materials and methods. The study was performed on the basis of the Department of Maxillofacial Surgery Poltava M.V. Sklifosovsky Regional Clinical Hospital. 90 patients with phlegmons of maxillofacial localization were under observation, which were divided into 2 observation groups (group 1 – patients who

got intravenous injections of the drug “Cryocel-hemocord” frozen suspension containing at least 500 IU/ml of alpha-fetoprotein is produced at the State Enterprise Interdepartmental Research Center for Cryobiology and Cryomedicine of the National Academy of Sciences, Academy of Medical Sciences, and the Ministry of Health of Ukraine, Kharkiv, Ukraine in the complex treatment; group 2 – patients who underwent intravenous injections of the drug “Cryocel-hemocord” in combination with topical application of cryopreserved placenta in the ointment Dioxomethyltetrahydropyrimidine + Chloramphenicol (“Levomecol”, Viola, Ukraine) on the basis of a standard treatment protocol Dioxomethyltetrahydropyrimidine + Chloramphenicol and 1 control group (with morning and evening chronotype). To achieve this purpose, patients were determined by the dynamics of changes of C-reactive protein in the blood serum.

For the treatment of phlegmon of the maxillofacial localization, a standard treatment protocol was used with the addition of 1.8 ml of cryopreserved placenta intravenously and its addition to the wound together with ointment Dioxomethyltetrahydropyrimidine + Chloramphenicol. The results of the study were processed by the method of variation statistics with a personal computer to determine the significance of differences between the values of the studied indices, as well as by the method of correlation using the software package Statistica and spreadsheets Excel 2010. The nonparametric Mann-Whitney test was used to determine the statistical significance of differences between the groups. The difference was considered statistically significant at $p < 0.05$.

Results of the study and their discussion. CRP is an evolutionarily conserved protein that is derived from arthropods to humans and is present in every organism. C-reactive protein is a plasma protein belonging to the group of acute phase proteins, the concentration of which increases during inflammation. It plays a protective role by binding the bacterial polysaccharide *Streptococcus pneumoniae*. C-reactive protein is used in clinical diagnostics along with ESR as an indicator of inflammation. C-reactive protein is an informative indicator of the acute phase of inflammation, the level of which at the stage of hospitalization of patients with odontogenic superficial phlegmons of maxillofacial localization was significantly increased (norm < 5 mg/l) and had no significant differences in both experimental and control groups (table 1).

Table 1

The content of C-reactive protein in the blood serum of patients with superficial odontogenic phlegmons of the maxillofacial localization, mg/l

Observation groups			Day 1	Day 3	Day 5	Day 7
Group 1	Subgroup 1	1a (n=8)	128.1±3.96	104.5±3.75 *	56.8±2.07 * **	38.0±1.20 * **
		1b (n=7)	127.6±4.08	110.3±2.87 *	68.4±2.17 * ***	45.3±1.36 * ***
	Subgroup 2	2a (n=8)	132.1±3.72	110.6±3.55 *	61.5±3.07 *	45.1±2.26 *
		2b (n=7)	129.7±4.01	105.0±5.17 *	57.6±2.77 *	41.1±2.08 *
	Subgroup 1	1a (n=8)	128.4±4.26	102.3±3.28 *	48.9±1.30 * ** ****	36.1±1.65 * **
		1b (n=7)	129.6±4.05	109.1±3.86 *	58.4±2.33 * ** ****	43.6±1.54 * ***
Group 2	Subgroup 2	2a (n=8)	127.8±3.74	109.8±2.96 *	58.9±2.16 *	44.3±1.73 *
		2b (n=7)	130.4±4.16	104.9±3.97 *	51.6±2.78 * **	36.7±1.48 * ** ****
	Subgroup 1	1a (n=8)	131.1±3.32	110.5±3.14 *	66.3±2.01 *	45.9±2.07 *
		1b (n=7)	128.9±3.35	111.1±3.49 *	70.1±3.00 *	50.3±2.88 *
Control group	Subgroup 2	2a (n=8)	133.0±3.25	113.3±3.83 *	69.0±4.14 *	48.6±2.58 *
		2b (n=7)	130.7±2.44	109.9±3.90 *	66.4±2.66 *	45.1±1.72 *

Notes: * $p < 0.05$ relative to the previous observation period; ** $p < 0.05$ relative to control for the same observation period; *** $p < 0.05$ when compared within one subgroup; **** $p < 0.05$ relative to the 1st experimental group.

On the third day of the observation in patients of the first experimental group under the conditions of intravenous injections of the drug is based on alpha-fetoprotein in the complex treatment of superficial odontogenic phlegmon of the maxillofacial area was marked a significant decrease of C-reactive protein level compared to the previous period by 18.4 %, 13.6 %, 16.3 % and 19.0 % for 1a, 1b, 2a and 2b subgroups.

For patients of the second experimental group, who underwent intravenous administration of the drug cryoextract of the placenta in combination with topical application of cryopreserved placenta in the

ointment Dioxomethyltetrahydropyrimidine + Chloramphenicol on the basis of a standard treatment protocol, a similar picture was observed, namely a significant reduction in C-reactive bi-protein. blood relative to the previous follow-up by 20.3 %, 15.9 %, 14.1 % and 19.6 % for the four subgroups.

In the control group, under the conditions of treatment according to standard protocols, there was also noted a significant decrease in the studied indicator in 1a, 1b, 2a and 2b subgroups relative to baseline data by 15.7 %, 13.9 %, 16.0 % and 15.9 % respectively.

Comparing the data of the two experimental and control groups, no significant differences in the content of C-reactive protein in the serum were observed at this stage of observation. The dependence of this index on the correspondence of the time of surgical treatment of phlegmon of maxillofacial localization and ligation to circadian rhythms of patients in all groups of supervision was not noted either.

On the 5th day of treatment, patients of the first experimental group showed a significant decrease in the content of C-reactive serum protein relative to the previous study period for 1a, 1b, 2a and 2b subgroups by 45.6 %, 38.0 %, 44.4 % and 45.1 % respectively.

The dependence of this index on the correspondence of the circadian rhythm of the time of surgery was established, which was manifested by a probable decrease in the content of C-reactive protein by 17.0 % in patients of morning chronotype who underwent surgery in the morning compared to those who underwent surgery in the evening. There was also noted a decrease in this index in patients of the morning chronotype, for whom the disclosure of phlegmon and dressings were performed in the morning relative to the control by 14.3 %.

In the analysis of the results of biochemical studies of patients who underwent intravenous injections of cryoextract of the placenta in combination with local administration of cryopreserved placenta in the ointment ointment Dioxomethyltetrahydropyrimidine + Chloramphenicol on the background of the standard protocol for the treatment of superficial odontogenic phlegmon in the maxillofacial area serum relative to the previous follow-up by 52.2 %, 46.5 %, 46.4 % and 50.8 % for all four subgroups, respectively.

In the case of compliance with the circadian rhythm of the time of surgical treatment, there was a significant decrease in the studied indicator relative to a similar subgroup in the control. For patients of the morning chronotype operated in the morning – by 26.2 %, for patients of the evening chronotype, who underwent surgery in the evening – by 22.3 %, respectively.

In patients of the morning chronotype at this stage of treatment there was a significant decrease in the studied indicator by 16.3 % during the opening of phlegmon and dressings in the morning relative to the evening time of these procedures. There was also a significant decrease in the content of C-reactive protein under the conditions of compliance of the time of surgery to the circadian rhythm in patients of the morning chronotype relative to a similar subgroup of the first experimental group by 13.9 %.

Patients treated with phlegmon according to standard protocols (control group) on the 5th day of follow-up showed a probable decrease in serum C- reactive protein relative to the previous study period by 40.0 %, 36.9 %, 39.1 % and 60.4 % for subgroups 1a, 1b, 2a and 2b, respectively. In this group there was no significant difference depending on the compliance of the time of surgery and dressings to the circadian rhythms of patients.

On the 7th day in experimental group 1 there was a decrease in the content of C-reactive protein in the serum compared to the previous study period by 33.1 %, 33.8 %, 26.7 % and 28.6 % for all four subgroups, respectively. There was also a significant decrease in the content of the studied indicator in patients of the morning chronotype, who underwent surgery in the morning relative to a similar subgroup in the control by 17.2 %.

Also in patients of the morning chronotype, the dependence of the time of treatment on the circadian rhythm was noted, namely a decrease in the content of C-reactive protein in patients operated on in the morning by 16.1 % compared to those who underwent surgery and dressings in the evening. No changes were observed in patients with evening chronotype at this stage of the study.

At this time of treatment in patients of the second experimental group who underwent intravenous injections of the drug cryoextract of the placenta in combination with topical administration of cryopreserved placenta in the ointment ointment Dioxomethyltetrahydropyrimidine + Chloramphenicol on the background of the standard protocol for the treatment of superficial odontogenic phlegmon maxillofacial significant reduction in the content of C-reactive serum protein by 26.2 %, 25.3 %, 24.8 % and 28.9 % for the four subgroups, respectively.

Analyzing the obtained data, the dependence of the content of the studied indicator on the correspondence of the time of treatment to the circadian rhythms of patients was established. In patients of the morning chronotype who underwent surgery in the morning and evening chronotype, who underwent surgical treatment and dressings of wound in the evening, there was a significant decrease in serum

C-reactive protein relative to similar control subgroups by 21.3 % and 18.6 %, respectively. Also for this period of observation, the dependence of this indicator on the time of surgical treatment relative to the circadian rhythms of patients was established. There was a significant decrease in the content of C-reactive protein under the conditions of compliance of the time of surgery to the circadian rhythms of the patient by 17.2 % for morning and evening chronotypes.

In the control group there was a significant decrease in the content of reactive protein in the serum relative to the previous observation period for all four subgroups by 30.8 %, 28.2 %, 29.6 % and 32.1 %, respectively. The dependence of the level of the studied indicator on the compliance of the time of surgery to the circadian rhythms of the patient was not noted.

Analyzing the indices of the acute phase of inflammation, in particular the level of C-reactive protein, it should be noted that at the beginning of treatment it is significantly increased and there were no probable differences in all 3 groups of observations, which corresponded to the literature [3, 11]. On the 3rd day in patients of the first and second experimental and control groups there was a significant decrease in this indicator relative to the previous study period. In clinical group 2 there was a decrease in the level of C-reactive protein by an average of 1.6 % compared to the first group, which is the evidence base for the effectiveness of combined use of cryopreserved placenta. The dependence of this index on the circadian rhythm for this period of observation has not been established in any clinical group. It is noteworthy that on the 5th day of the postoperative period, the percentage of significant decrease increases significantly and in the first group reaches relative to the previous observation period for subgroups of groups 1 and 2. The dependence of this index on the correspondence of the circadian rhythm of the time of opening and drainage of the purulent center is established [7].

The best results on a significant decrease in C-reactive protein in the serum were recorded in patients of group 2. It should be noted that a significant decrease in this indicator relative to a similar subgroup in the control was recorded in patients under conditions of compliance with the time of surgery chronotype. On the 7th day of the postoperative period there was a decrease in serum C-reactive protein relative to the previous observation period, but approaching the norm in 92 % of cases was recorded in patients of group 2 and 79.5 % in patients of group 1, which is evidence of the effectiveness of methods of conservative treatment.

Conclusion

Thus, analyzing the results of the studies, in all observation groups there was a significant increase in the content of C-reactive serum protein at the time of hospitalization of patients with superficial odontogenic phlegmons of maxillofacial localization before surgery and medication. In all groups during the therapy there was a tendency to reduce the level of this indicator. For patients of the morning chronotype operated in the morning – by 26.2 %, for patients of the evening chronotype, who underwent surgery in the evening – by 22.3 %, respectively. The most pronounced changes were observed in the first and second experimental groups, under the conditions of intravenous administration of the cryoextract placenta and its combination with local administration of cryopreserved placenta in the ointment of levomicetin based on standard treatment protocols for these diseases.

It should be noted that the dynamics of changes in the parameters of reactive serum protein on the compliance of the time of surgery and ligation of circadian rhythms of patients in the experimental groups, which was characteristic of later treatment of patients with phlegmons of maxillofacial localization and was not observed in early treatment, while similar changes were not observed in the analysis of data from the control group of patients.

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INNATE IMMUNITY IN OSTEOARTHRITIS IN COMORBIDITY WITH NON-ALCOHOLIC STEATOHEPATITIS IN PATIENTS WITH *HELICOBACTER PYLORI* INFECTION

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The pathogenesis of comorbid pathology of joints and liver in patients infected with *Helicobacter pylori* is considered in the study. We examined 57 patients with osteoarthritis in comorbidity with non-alcoholic steatohepatitis, of whom 23 showed specific antibodies to *Helicobacter pylori* without clinical and instrumental manifestations of gastric and duodenal mucosa. The study revealed a decrease in phagocytic activity of monocytes, the number of populations of NK lymphocytes, which can be characterized as a lack of nonspecific reactivity in the examined patients. There was a significant decrease in phagocytic activity of monocytes with activation of nonspecific reactivity of the body (increase in the number of NK lymphocytes), growth of serum proinflammatory (IL-8, IL-12) cytokines, against the background of *Helicobacter pylori* infection in osteoarthritis in comorbidity with non-alcoholic steatohepatitis, indicating the presence of chronic systemic inflammation. The study of the level of cytokines and innate immune factors in the comorbid course of osteoarthritis and non-alcoholic steatohepatitis on the background of *Helicobacter pylori* infection can be used to predict the further progression of the inflammatory reaction in the liver, the intensity of immunopathological reactions in the joints and the development of pathogenetic therapy methods of the specified category of patients.

Key words: osteoarthritis, non-alcoholic steatohepatitis, *Helicobacter pylori*, innate immunity, phagocytic activity of monocytes, cytokines.

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СТАН ВРОДЖЕНОГО ІМУНІТЕТУ ПРИ ОСТЕОАРТРОЗІ В КОМОРБІДНОСТІ З НЕАЛКОГОЛЬНИМ СТЕАТОГЕПАТИТОМ У ХВОРИХ НА ХЕЛІКОБАКТЕРІОЗ

В статті розглянуто питання патогенезу коморбідної патології суглобів та печінки у хворих, інфікованих *Helicobacter pylori*. Обстежено 57 хворих на остеоартроз в коморбідності з неалкогольним стеатогепатитом, з яких у 23 осіб виявлено специфічні антитіла до *Helicobacter pylori* без клініко-інструментальних проявів ураження слизової оболонки шлунка та дванадцятипалої кишки. В результаті дослідження встановлено зменшення показників фагоцитарної активності моноцитів, кількості популяції NK-лімфоцитів, що можна характеризувати як недостатність неспецифічної реактивності організму в обстежених хворих. На фоні інфікування *Helicobacter pylori* при остеоартрозі в коморбідності з неалкогольним стеатогепатитом відмічалось суттєве зменшення показників фагоцитарної активності моноцитів з активацією неспецифічної реактивності організму (збільшення кількості NK-лімфоцитів), зростання сироваткових прозапальних (IL-8, IL-12) цитокінів, що свідчить про наявність хронічного системного запалення. Дослідження рівня цитокінів і факторів вродженого імунітету при коморбідному перебігу остеоартрозу та неалкогольного стеатогепатиту на фоні хелікобактеріозу можна використовувати для прогнозування подальшого прогресування запальної реакції в печінці, інтенсивності імунопатологічних реакцій у суглобах та розробки методів патогенетичної терапії означеної категорії хворих.

Ключові слова: остеоартроз, неалкогольний стеатогепатит, *Helicobacter pylori*, вроджений імунітет, фагоцитарна активність моноцитів, цитокіни.

The work is a fragment of the research project "Features of pathogenesis and optimization of treatment of patients with comorbid pathology on the background of Helicobacter pylori infection", state registration No. 0118U000822.

Despite the urgency of the problem, there is still no consensus on the pathogenesis of osteoarthritis (OA). For a long time, OA was considered a non-inflammatory disease that is associated with degeneration of cartilage tissue, without its regeneration. Chronicity of the pathological process in the joint leads to the progression of the secondary alteration of hyaline cartilage, and the decay products of cartilage (fragments of collagen and proteoglycans) enter the synovial fluid, developing and intensifying the inflammatory response in the joint, which leads to a predominance of catabolic processes in the cartilage [9, 14]. The content of cytokines in the serum depends on the involvement of systemic immune responses to the