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ЦИРКУЛИРУЮЩИЕ БИОМАРКЕРЫ СИСТЕМНОГО ВОСПАЛИТЕЛЬНОГО ОТВЕТА В ОЦЕНКЕ ПОСТПЕРИКАРДИОТОМИЧЕСКОГО СИНДРОМА У ПАЦИЕНТОВ ПОСЛЕ КАРДИОХИРУРГИЧЕСКИХ ВМЕШАТЕЛЬСТВ

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Резюме. В настоящее время одним из частых осложнений, регистрируемых у 9-65% пациентов после кардиохирургического вмешательства, является постперикардиотомический синдром (ПКТС). Несмотря на широкую распространенность, механизмы развития ПКТС до сих пор мало изучены. Особенный интерес представляет использование колхицина, являющегося мощным противовоспалительный препаратом. Предполагаемые механизмы действия данного препарата обусловлены способностью колхицина ингибировать мобилизацию сборки инфламмасомы NLRP3, подавлять активацию каспазы-1 и, как следствие, предотвращать высвобождение провоспалительных цитокинов. На сегодняшний день имеются противоречивые данные об использовании колхицина и его влиянии на развитие ПКТС в рамках системного воспалительного ответа после кардиохирургических вмешательств. В связи с этим актуальным представлялось изучить динамику сывороточного содержания IL-6, IL-10, IL-1β, TNFα у пациентов перед аортокоронарным шунтированием (Т1), через 6 ч (Т2), на 10-е сутки (Т3) после операции и оценить влияние колхицина на развитие постперикардиотомического синдрома. Анализ цитокинового профиля показал, что в обеих группах через 6 ч после операции отмечался пик высвобождения в кровоток IL-10 с последующим снижением к 10-м суткам, но в группе 1 уровень IL-10 оказался выше исходных значений, чем в группе 2. В обеих группах содержание IL-6 многократно повышалось на Т2 и значимо снижалось к Т3, при этом уровни IL-6 в группе 2 оставались выше по сравнению с исходными значениями. Частота развития плеврита была ниже в группе пациентов, принимающих колхицин. Только в группе 1 показаны положительные корреляционные связи между IL-6 и TNFα. У пациентов без признаков плеврита уровень IL-10 напрямую ассоциировался с повышенным содержанием TNFα. Не было выявлено значимых межгрупповых отличий сывороточного уровня IL-1β и TNFα, а также значимых изменений IL-1β между этапами наблюдения. Анализ экспрессии TNFα выявил в группе 1 значимые отличия содержания TNFα между этапами Т1-Т3 и Т2-Т3 ($p < 0,05$). В обеих группах были установлены множественные позитивные ассоциации между изучаемыми показателями. Таким образом, полученные данные свидетельствуют

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о противовоспалительном эффекте колхицина у кардиохирургических больных. Клинически это выражалось в тенденции к меньшей частоте развития плевритов и сопровождалось повышенной экспрессией IL-10, обладающего противовоспалительным и иммуномодулирующим действием на фоне приема препарата в послеоперационном периоде.

Ключевые слова: колхицин, кардиохирургические вмешательства, постперикардиотомический синдром, плеврит, системный воспалительный ответ

CIRCULATING BIOMARKERS OF SYSTEMIC INFLAMMATORY RESPONSE IN THE ASSESSMENT OF POSTPERICARDIOTOMY SYNDROME IN PATIENTS AFTER CARDIAC SURGERY

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Abstract. Postpericardiotomy syndrome (PCTS) is one of the most frequent cardiac surgery complications seen in 9-65% of patients. Despite its widespread occurrence, the mechanisms of the development of PCTS are still understudied. drug. The use of colchicine in cardiac surgery patients is of particular interest. Due to the ability of this drug the colchicine mechanisms of action are able to inhibit the mobilization of the NLRP3 inflammasome assembly, to suppress the activation of caspase-1. As a result, it can prevent the release of pro-inflammatory cytokines, namely IL-1β and IL-18. There are conflicting data on the effect of colchicine on the PCTS progression within the systemic inflammatory response after cardiac surgery. In this regard, it was important to study the dynamics of serum levels of IL-6, IL-10, IL-1β, and TNFα in patients before coronary artery bypass grafting (T1), 6 hours (T2), and 10 days (T3) after surgery, and to evaluate the effect of colchicine on the development of PCTS. The results of our research showed a significant increase of IL-10 in both groups 6 hours after surgery. However, on the 10th day, the increase in the level of IL-10, compared with the initial values, was higher in the 1st group – 2 times, compared with the 2nd group. In both groups, showed significant increase in serum concentration of IL-6 after 6 h surgery, with a subsequent decrease in the expression at the stage of T3, while the IL-6 levels in the 2nd group was statistically notably higher than T1. The incidence of pleurisy was lower in the group of patients taking colchicine. Only in the 1st group IL-6 levels were directly associated with IL-10. In patients with pleurisy, the level of released IL-10 and TNFα was significantly higher in the 2nd group. There were no significant intergroup differences in serum levels of IL-1β and TNFα, as well as significant changes in IL-1β between the stages of observation. Analysis of TNFα expression revealed significant differences in TNFα content in the 1st group between the T1-T3 and T2-T3 stages. In both groups, multiple positive associations were found between the studied indicators. Thus, data were obtained indicating the anti-inflammatory effect of colchicine in cardiac surgery patients. This was clinically expressed in a tendency to a lower incidence of pleurisy, and was accompanied by increased expression of IL-10, which has an anti-inflammatory and immunomodulatory effect against the background of the drug in the postoperative period.

Keywords: colchicine, cardiac surgery, postpericardiotomy syndrome, pleurisy, systemic inflammatory response

Introduction

Coronary artery disease (CAD) is a common disease of the cardiovascular system, accompanied by a high risk of vascular complications and death. Currently, coronary artery bypass grafting (CABG) is one of the most effective treatment methods for patients with multifocal atherosclerosis of the coronary arteries and complicated CAD forms.

The CAD excess incidence, the number and complexity of CABG operations makes it necessary to improve the safety and effectiveness of surgical intervention, identify predictors of development, impro-

ve early diagnostics methods and develop new approaches to prevent cardiac surgical complications. Postpericardiotomy syndrome (PCTS) is one of the most frequent cardiac surgery complications observed in 9-65% of patients [13, 14]. Despite its widespread occurrence, the mechanisms of developing PCTS are still understudied.

During operations with artificial blood circulation, many aggressive factors are experienced, including surgical trauma, exposure to cardioplegia, hypothermia, ischemic/reperfusion injury, blood contact with bioactive surfaces of the circuit in the artificial blood circulation apparatus, which leads to the launched inflammatory reaction, including the activation of proteins and blood plasma cells, the release of pro-inflammatory molecules, enzymes and cytotoxic substances [9, 12, 15]. Extensive research was conducted for studying preventive treatment of patients with cardiac surgery. There were used drugs with anti-inflammatory effects that affect various stages of PCTS formation. At the moment, all drugs that were used for treatment of both PCTS and pericarditis are "off-label", i.e. initially, they were not registered for treatment of such pathologies. In this regard, the use of colchicine in cardiac surgery patients is of particular interest as a powerful anti-inflammatory drug traditionally used for gout treating. Due to the ability of this drug, the colchicine mechanism of action is able to inhibit the mobilization of the NLRP3 inflammasome assembly and suppress the activation of caspase-1. As a result, it can prevent the release of pro-inflammatory cytokines, namely IL-1β and IL-18. The drug has an antimitotic effect, suppresses (fully or partly) cell division in the anaphase and metaphase stages, prevents neutrophil degranulation and reduces migration of white blood cells to the focus of inflammation [4, 11]. It is known that by interfering with the microtubule polymerization, colchicine inhibits the chemotaxis of monocytes and neutrophils, which are found in large numbers in the lungs of patients with COVID-19 [1]. Currently, several randomized trials are ongoing to evaluate the feasibility of using colchicine in patients with COVID-19. Among them, COLCORONA – a large-cohort study involving patients with cardiac manifestation of COVID-19 and a smaller study COLHEART-19, which includes hospitalized patients. To this date, conflicting data have been obtained on the use of colchicine, including cardiac surgery patients. During the study [1], colchicine was used in hospitalized patients with severe COVID-19 to prevent a "cytokine storm". The first COLORIT results emphasizing the effectiveness of colchicine (at a dose of 1 mg for 1-3 days, with the following treatment at a dose of 0.5 mg/day for 14 days) as a proactive anti-inflammatory therapy in hospitalized patients with COVID-19 and viral pneumonia have been obtained [3]. The results of the first LoDoCo research involving 532 individuals demonstrated the efficacy, safety, and long-term tolerability of colchicine (0.5 mg once daily), as well as improved cardiovascular outcomes in patients with chronic CAD [7]. The COPPS study showed that colchicine significantly reduced the incidence of pericarditis for 12 months compared to placebo (12.2% *vs* 25.6%, $p = 0.002$) in cardiac surgery patients, however, in the COPPS-2 research, prescription of colchicine for 48 and 72 hours before surgery did not reduce the incidence of postoperative pericarditis compared to placebo [2]. In the POPE-2 study: colchicine prescription to patients after cardiac surgery did not reduce the volume of effusion in the pericardium [10]. The results of the COLCOT research showed that low doses of colchicine reduce the risk of recurrent cardiovascular events in patients with recent myocardial infarction [5]. At the same time, controversial data on the effect of colchicine on the PCTS progression during systemic inflammatory response after cardiac surgery were obtained.

Objective: to study the dynamics of inflammatory response markers in patients after coronary artery bypass grafting and evaluate an effect of colchicine on the developing postpericardiotomy syndrome.

Materials and methods

There were enrolled 84 patients (aged 62.5±6.7 years) with a coronary artery disease diagnosis, angina pectoris (functional class II-III), with multivessel stenosing coronary atherosclerosis. All patients were hospitalized at the Department of Cardiovascular Surgery of the Research Institute of Cardiology for performing CABG under conditions of artificial blood circulation. The exclusion criteria were: reduced left ventricular ejection fraction (≤ 35%), valvular pathology requiring surgical correction, hepatic insufficiency with increased level of hepatic transaminases by ≥ 1.5 times, renal insufficiency (increased creatinine levels of more than 130 mmol/L), persistent or persistent form of atrial fibrillation, hypersensitivity, neutropenia, and a history of alcoholism. The research protocol was approved by the local ethics committee.

Patients were divided into two groups: group 1 ($n = 45$), in order to prevent postoperative complications, colchicine was prescribed at a dose of 0.5 mg once per 4 hours before surgery, followed by 0.5 mg twice a day for 10 days after surgery; group 2 ($n = 39$) received standard treatment with nonsteroidal anti-inflammatory drugs (NSAID) after surgery.

The dynamics of biomarkers of the systemic inflammatory response were evaluated before CABG (T1), as well as 6 hours (T2), and 10 days (T3) after surgery. In all patients, the ulnar vein was punctured in the morning within the followup period. Blood samples were collected and incubated at room temperature for 30-45 minutes followed by centrifuge at 3000 rpm for 15 minutes at room temperature. The serum levels of interleukins 6 (IL-6), 10 (IL-10), 1-β (IL-1β), and tumor necrosis factor (TNFα) were measured by multiplex immunoassay using MILLIPLEX® MAP KIT (Merck KGaA, Darmstadt) and FLEXMAP 3D System (Luminex® Corporation) diagnostic panels.

In the preoperative and postoperative periods, all patients underwent a set of laboratory tests, including measurement of C-reactive protein, white blood cell count, and specific enzymes (AST, ALT, creatinine). In the postoperative period, fluid accumulation in the pleural cavities and in the pericardium were daily monitored.

Statistical processing of the data obtained was performed by using the Statistica 10.0 application software package. Due to the data differed from the normal distribution, all quantitative parameters were described by using the median (Me) and interquartile range ($Q_{0.25}$-$Q_{0.75}$). For pairwise comparison, the Kruskal–Wallis rank criterion was used. The statistical significance of the differences was evaluated by using the nonparametric Wilcoxon test. The Spearman rank correlation coefficient was calculated to assess inter-parameter relationship. In all statistical analysis procedures, the critical significance level of p is assumed to be 0.05.

Results and discussion

According to the results of the routine tests and clinical data in the preoperative period, no signs of inflammation in patients from both groups were found. Table 1 shows the results of quantitative analysis of expressed cytokines before CABG (T1), as well as 6 hours (T2) and 10 days (T3) after surgery (Table 1).

Despite the fact that at the time of inclusion in the study for the main disease, types of surgical correction, duration of surgery and artificial blood circulation, as well as other comorbidities of the group, both groups were comparable, while analyzing the level of IL-10, significant differences were initially revealed in group 1 *vs* group 2, being markedly elevated by about 2-fold. Further, 6 hours after the operation, we noted its significant increase in both groups. However, on day 10 *vs* baseline, an increased level of IL-10 was higher in group 1 *vs* group 2 by 2-fold.

The results of our research also showed significantly increased serum concentration of IL-6 6 hrs after surgery that subsequently decreased at the stage of T3, with varying degrees of severity: in group 1 level of IL-6 did not differ from baseline values, but in group 2 was significantly higher than at T1 ($p = 0.0005$).

The results of the comparative analysis revealed no statistically significant intergroup difference in serum

TABLE 1. DYNAMICS OF INFLAMMATORY RESPONSE BIOMARKERS BEFORE CORONARY ARTERY BYPASS GRAFTING (T1), 6 HOURS (T2) AND 10 DAYS (T3) AFTER SURGERY, Me ($Q_{0.25}$-$Q_{0.75}$)

	Group 1 (n = 44)			p	Group 2 (n = 39)			p	p between groups
	T1	T2	T3		T1	T2	T3		
IL-10, pg/ml	1.95 (1.18-4.52)# * **	15.75 (9.86-59.49)***	3.90 (2.30-8.37)#	$p_{T1-T2} < 0.000$ $p_{T2-T3} < 0.000$ $p_{T1-T3} < 0.000$	1.01 (0.56-2.41)# *	14.93 (7.25-33.02)***	1.66 (0.75-3.30)#	$p_{T1-T2} < 0.000$ $p_{T2-T3} < 0.000$	$p_{T1} = 0.007$ $p_{T3} < 0.000$
IL-1β, pg/ml	0.39 (0.28-0.62)	0.49 (0.32-0.67)	0.42 (0.30-0.58)	N/D	0.46 (0.27-0.90)	0.46 (0.30-0.70)	0.45 (0.30-0.61)	N/D	N/D
IL-6, pg/ml	0.52 (0.04-3.47)*	61.54 (42.05-86.58)***	2.09 (0.82-5.74)	$p_{T1-T2} < 0.000$ $p_{T2-T3} < 0.000$	0.17 (0.10-0.70)* **	46.45 (33.05-73.39)***	2.63 (1.13-5.33)	$p_{T1-T2} < 0.000$ $p_{T2-T3} < 0.000$ $p_{T1-T3} < 0.000$	N/D
TNFα, pg/ml	13.49 (7.19-19.18)**	12.42 (6.03-19.95)***	17.13 (8.38-23.20)	$p_{T1-T3} = 0.036$ $p_{T2-T3} = 0.036$	11.71 (7.63-14.55)	9.86 (4.15-14.60)	10.39 (6.42-19.52)	N/D	N/D
IL-10/ TNFα	0.23 (0.10-0.41)# * **	1.45 (0.76-6.74)***	0.33 (0.16-0.84)#	$p_{T1-T2} < 0.000$ $p_{T2-T3} < 0.000$ $p_{T1-T3} = 0.020$	0.13 (0.05-0.28)# *	2.07 (0.84-3.93)***	0.18 (0.09-0.36)#	$p_{T1-T2} < 0.000$ $p_{T2-T3} < 0.000$	$p_{T1} = 0.024$ $p_{T3} = 0.019$

Note. The difference (p < 0.05): *, between T1 – T2; **, between T1-T3; *, between T2-T3. Intergroup statistically significant (p < 0.05) differences: #, p < 0.05; N/D, not detected.**

TABLE 2. INFLAMMATION RESPONSE BIOMARKERS IN PATIENTS WITH PLEURISY

Pleurisy			
Cytokines	**Group 1 (n = 10)**	**Group 2 (n = 14)**	**p**
IL-10 (T1), pg/ml	2.17 (1.43-3.51)	0.66 (0.10-1.66)	p = 0.006
TNFα (T3), pg/ml	20.56 (13.05-23.06)	8.73 (7.62-13.59)	p = 0.004
Without pleurisy			
	Group 1 (n = 34)	**Group 2 (n = 25)**	
IL-10 (T3), pg/ml	3.68 (2.44-8.73)	1.71 (0.48-3.34)	p = 0.003
IL-10/TNFα (T3)	0.41 (0.16-0.97)	0.13 (0.09-0.32)	p = 0.009

levels of IL-1β, as well as significant changes in IL-1β between the stages of observation ($p > 0.05$).

Comparative analysis of TNFα expression showed no differences between the studied groups, but revealed the peculiarities in its dynamics between the stages of observation. Thus, in group 1, the peak of TNFα release was observed 10 days after surgery. Significant differences in the TNFα level were found between the T1-T3 and T2-T3 stages ($p < 0.05$). In group 2, the serum TNFα level did not differ between the stages.

Our study revealed significant inter-group differences in the IL-10/TNFα index: patients receiving colchicine had IL-10/TNFα ratio significantly higher at stages T1 and T3 *vs* group 2 ($p = 0.024$ and 0.019, respectively). In both groups, a maximum of IL-10/TNFα ratio was observed 6 hours after surgery. 10 days after CABG, the magnitude of this parameter in group 1 remained markedly elevated compared to baseline level at T1 ($p = 0.02$).

In the group of patients receiving colchicine, the incidence of pleurisy was lower than in the group with NSAID (22.2% and 35.9%, respectively). The results of the comparative analysis showed that patients with pleurisy had the level of IL-10 and TNFα significantly elevated in group 1 (Table 2).

In both groups, multiple positive associations were found between the studied indicators. Thus, a high level of IL-10 released into the bloodstream was associated with increased amount of TNFα at all stages of the follow-up period. Similar correlations were shown for IL-6 and IL-1β, as well as IL-10/TNFα and IL-6 at stage T1. Only in the group of patients receiving colchicine, the correlation analysis showed positive associations between IL-6 and TNFα. IL-6 levels were directly associated with IL-10 in group 1 at 6 hrs, whereas in group 2 – at day 10 after surgery. Patients without signs of pleurisy in both groups had the level of released IL-10 that was directly associated with increased level of TNFα, while this relationship was not found in patients with pleurisy.

Direct traumatization of the pericardial leaflets, ischemic (during anoxia) and reperfusion (after removing the clamp from the aorta) damage to cardiomyocytes, hypothermia, and contact of blood cell elements with the surface of the artificial circulatory apparatus are considered as triggers that contribute to development of systemic inflammation in the postoperative period [15]. In addition, in the first hours of the postoperative period, there is a high probability of bleeding into the pericardial cavity, which also serves as a trigger for the inflammatory process [12]. The action of damaging factors leads to the activation of immunocompetent cells, as well as release of inflammatory mediators into the systemic bloodstream, which contribute to developing local and systemic inflammatory reactions.

In our study, the analysis of the cytokine profile of cardiac surgery patients showed that in both groups, 6 hours after surgery, the release of IL-10 into the bloodstream, which has anti-inflammatory and immunosuppressive properties, controlling the severity and duration of the inflammatory process was at peak. In addition, 10 days after CABG, the level of IL-10 decreased, but in group 1, its increase to the baseline magnitude was higher than in group 2.

IL-1β and TNFα are proinflammatory cytokines, which potentiate intensity of inflammatory process manifested by increased exudation and mobilization of neutrophils in the focus of inflammation. High levels of such cytokines immediately after exposure to the damaging factor are necessary for formation of proper inflammatory response, but their production should decline later. TNFα levels *vs* other cytokines rise early that reflects its role as an initiator in the inflammatory response. TNFα is a mediator of various pathologies and involved in the "cytokine storm" [14]. The results of our study revealed no significant inter-group differences in serum IL-1β levels, as well as significant changes in IL-1β between follow-up stages. Comparative analysis of TNFα expression also showed no differences between the

studied groups. It is recognized that chronic diseases are a significant factor that reduces the level of proinflammatory cytokines. The absence of marked changes in the dynamics of IL-1β and TNFα in our study seem to be connected to the chronic nature of the underlying disease.

IL-6 acts as an indicator of the intensity in the inflammatory process. In cardiac surgery, IL-6 is produced mainly in the myocardium. Plasma levels of IL-6 correspond to the severity of tissue damage caused by surgical trauma and the severity of inflammatory response caused by artificial blood circulation. IL-6 also has a high predictive value for 30-day and total mortality in patients after cardiac surgery. In our study, the IL-6 level increased frequently 6 hours later and notably decreased by day 10 after surgery, while the levels of IL-6 in group 2 remained elevated compared to the baseline magnitude.

The serum IL-10/TNFα ratio is an indicator of inflammatory response and a prognostic sign of the severity and outcome of the infectious process [15]. In our study, the magnitude of IL-10/TNFα ratio in the group of patients receiving colchicine *vs* group 2 was markedly higher at the T1 and T3 stages. A maximum of IL-10/TNFα ratio was observed 6 hours after surgery in both groups. 10 days after CABG, its magnitude in group 1 remained significantly elevated compared to baseline level.

The incidence of pleurisy in our study was lower in the group of patients receiving colchicine, but did not significantly differ from that one in group 2. The results of the comparative analysis showed that in patients with pleurisy, the level of released IL-10 and TNFα was significantly higher in the group 2. It is necessary to take into account that the biological effects of many cytokines have a high degree of redundancy, which creates wide opportunities to compensate for the insufficiency or deficiency of some mediators, as well as many cytokines are able to interact with components of the same receptor complexes.

Only in the group of patients receiving colchicine, the correlation analysis showed the positive association between IL-6 and TNFα. IL-6 levels were directly associated with IL-10 in group 1 at 6 hrs, whereas in group 2 – at day 10 after surgery. In patients without signs of pleurisy in both groups, the level of released IL-10 was directly associated with increased level of TNFα, while this relationship was not found in subjects with detected pleurisy.

Thus, the data obtained indicate that colchicine had anti-inflammatory effect in cardiac surgery patients clinically manifested as a tendency to lower incidence of pleurisy and accompanied by increased expression of IL-10 exerting anti-inflammatory and immunomodulatory effect compared to the postoperative period.

A comprehensive assessment of the dynamics for pro-and anti-inflammatory cytokines can be used for studying features of inflammatory response and preventing development of postoperative complications in cardiac surgery patients.

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