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Effect of Acetylcystene on Endothelic Activity and Immuno-Inflammatory Processes in Acute Coronary Syndrome

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Abstract. The study involved 100 hospitalized patients diagnosed with ACS in the form of ST segment elevation on an electrocardiogram at the age of 58.4 ± 10.5 years. In accordance with the tactics of treatment, they were divided into control (n = 50) and base (n = 50) groups. The control group was divided into two groups: patients receiving basal therapy (BT) in group I (n = 25) and coronary angioplasty (CA) in group II (n = 25).Therefore, the main group was assigned N-acetylcysteine (ACC) for 10 days. They were also divided into two groups and selected patients who received BT + ACC for group III (n = 25) and CA + ACC for group IV (n = 50). According to the results, the use of BT + ACC and CA + ACC from the first hours in patients after myocardial infarction has a positive effect on improving endothelial function by correcting the imbalance of the NO-system. At the same time, there is an improvement in the inflammatory process based on hypercytokinemia, that is, the cessation of IL-6 aggression. In addition, along with the improvement of hemodynamic parameters, it helps to restore the activity of the endothelium.

Key words: acute coronary syndrome, endothelial dysfunction, cytokines.

Despite the rapid development of practical medicine today, chronic diseases of the cardiovascular system are big problems in the practice of practical medicine. In particular, coronary heart disease (CHD), one of the leading causes of permanent or long-term disability, is characterized by various clinical manifestations and characteristics, especially in middle-aged patients, which leads to early disability and high mortality, which determines the social significance and urgency of the problem [10 , 20]. This can be explained by the fact that its progression, like various diseases, depends on the pathogenesis and treatment of the disease [4, 7, 18], starting from the negative impact of environmental factors on it [3].

The widespread use of modern antianginal, antiplatelet and hypolipedaemic drugs in coronary artery disease leads to increase in therapeutic efficacy [1, 18]. However, due to the limited possibilities of conservative treatment to improve the quality of life, interventional managements such as coronary angioplasty (CA) and stenting are now widely used. Although today the method and technology of CA are constantly being coordinated, postoperative complications and problems remain in patients with coronary artery disease [21]. In 14.6% of patients who underwent percutaneous revascularization with stenting and received appropriate

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drug therapy, including antithrombotic therapy, statins, angiotensin converter enzyme inhibitors / angiotensin receptor antagonists, b-blockers, vascular events occurred in 14.6% of patients, i.e. ... repeated myocardial infarction. Hospitalizations due to ACS, revascularization, and cardiac death have been reported [4, 16]. 2 years after ACS, these phenomena occur in 25% of patients, and after 4 years - in almost 40%. According to international registries, mortality 6 months after ACS reaches 12.1%, and after 2 years - 17.8% [10, 16]. In addition, the observation of problems such as dissection of the intimacy of vessels, restenosis of the coronary arteries and intravascular coagulation, as well as thrombosis, opens up new possibilities. It should be noted that in recent years [9] vascular endothelial dysfunction is one of the leading pathogenetic mechanisms of the disease in the formation and progression of atherosclerosis. Indeed, it is important to demonstrate endothelial dysfunction (ED), which is considered as a universal mechanism for the development and progression of coronary artery disease under the influence of risk factors. Today it is known that impaired endothelial function depends on the localization of the pathological process, the state of hemodynamic changes and various factors [19, 21]. Therefore, it is advisable to use agents that affect ED [17]. It should be noted that recently, more and more attention is paid to N-acetylcysteine, which contains a low molecular weight thiol and has antioxidant properties.

According to a lot of literature, N-acetylcysteine protects body cells from free radicals by reacting directly with them and providing cysteine for the synthesis of glutathione [23]. It was reported [22] that N-acetylcysteine helps to restore the activity of the left ventricle in patients with myocardial infarction. Subsequent observations made it possible to formulate the principles of action of N-acetylcysteine in emergency conditions in cardiological practice. In this case, it has a positive effect on platelet function, participates in the suppression of angiotensin, a converting enzyme and modulates the effect on coagulation and adhesion processes, and also has antiarrhythmic properties. In particular, scientific studies of the possibility of using N-acetylcysteine in ACS appear in the literature.

N-acetylcysteine is a "purifier" of active forms of nitrogen - nitric oxide and peroxynitrite, i.e. its application allows to achieve not only "oxidative", but also "nitrating" stress relief. In addition, N-acetylcysteine reduces the deposition of nitric oxide due to its effect on the formation of nitric oxide, carried out by the enzyme NO-synthase, and leads to a change in the type of molecular label for it [23]. Therefore, given that N-acetylcysteine is a substance that modulates nitric oxide, that is, causes it to increase or decrease, it is of practical importance to study its effect on ED in ACS.

Goal of research: to assess the dynamics of endothelial activity and immune-inflammatory parameters under the influence of acetylcysteine in ACS.

Materials and research methods. We examined 100 patients aged 41 to 68 years (58.4 ± 10.5) with a ST-segment elevation electrocardiogram obtained in the intensive care unit of the Russian Scientific Center for Emergency Medicine. Subsequently, patients underwent transformation of acute myocardial infarction

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with Q deflection in 62% of cases and myocardial infarction with Q deflection in 28%.

ACS diagnosis is based on ESH / ESC guidelines (2013). All patients underwent tests including electrocardiography (ECG) and echocardiography (EchoKG), taking into account such characteristics as lifestyle, diet, smoking, duration of the disease, heredity and level of physical activity [2].

Endothelial activity was assessed chromatographically based on potentiometric determination of plasma and erythrocyte nitrate (NO3) levels and plasma L-arginine levels. Immunoassays for IL 1b, IL 6 and TNF-a were used to study the immune-inflammatory process. Alternatively, based on the Doppler data of the right brachial artery, it was assessed using the D. S. Celemajer method [5] using the reactive hyperemia test. Changes in the readings of the right brachial artery were assessed using a 7 MHz linear detector with a phase grid of the Acuson 128 ultrasound system (USA). The diameter of the right brachial artery (D, cm), systolic (Vs), diastolic (Vd) and mean (Vmean) blood flow velocity (m / s) in the right brachial artery were studied.

All ACS patients were divided into control and baseline groups according to the treatment method, and they were approximately correlated in terms of age, sex and other parameters (Table 1).

The control group (n = 50) consisted of 58.1 ± 6.8-year-old patients with ACS with ECG ST elevation using traditional tactics. In turn, they were divided into two groups, conventionally called groups I and II:

Group I (n = 25) included patients who underwent the following basic treatment (BD) measures in an inpatient setting:

- Peaceful situation;
- Thrombolytic therapy (first 3 hours)
- b-blocker (Metoprolol 100-200 mg once a day)
- Nitrate drug (Izoket intravenous infusion 10-15 mcg / minute);
- Acetylsalicylic acid 325 mg;
- Enoxaparin subcutaneously 1 mg / kg 2 times a day.

Group II (n = 25) included patients who underwent coronary angioplasty (TA). Standard treatments (anticoagulants, antiaggregants, b-adrenoblockers, statins, etc.) were used for all patients.

The main groups (n = 50) were 59.3 ± 7.4 patients with ST ACS using N-acetylcysteine (AC) based on the basic treatment method. In turn, they were also divided into two groups, conventionally called groups III and IV:

Group III (n = 25) included patients with BT-based CA (BT + ACC).

Group IV (n = 25) included patients with AC-based CA (AC + ACC).

N-acetylcysteine (ACC) was administered in tablet form at 600 mg daily for 10 days.

Criteria for exclusion from the study:

- cardiogenic shock, recurrent myocardial infarction, heart defects, acute cerebrovascular disorders, renal and hepatic insufficiency, pulmonary and bronchial diseases, severe diabetes and arrhythmias;

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- Presence of an observed allergic reaction to the drug N-acetylcysteine (AC) or its component.

Table 1

Clinical description of the patients involved in the study

Indicators	Group I (n=25)	Group II (n=25)	Group III (n=25)	Group IV (n=25)
Patient age	56,1±6,1	59,1±4,9	59,7±5,4	58,1±6,4
Men	11 (44)	8 (32)	12 (48)	10 (40)
Women	14 (56)	17 (68)	13 (52)	15 (60)
Duration of CHD (years)	4,1±0,22	3,3±0,21	3,6±0,21	2,9±0,21
Smokers (%)	13 (52)	11 (44)	12 (48)	14 (56)
The duration of AG	3,3±0,5	4,4±0,3	4,3±0,2	3,4±0,4
Body mass index	26,1±0,51	27,2±0,62	25,9±0,55	27,3±0,66
Total cholesterol (mmol / l)	6,9±0,93	7,2±0,88	7,8±0,76	7,9±0,69
CHS HDLP (mmol / l)	0,89±0,19	0,94±0,66	0,82±0,52	0,93±0,69
CHS LDLP (mmol / l)	4,8±0,81	4,9±0,69	5,2±0,97	4,7±0,78
TG (mmol / l)	2,39±0,28	2,53±0,68	2,12±0,58	2,52±0,39

Note: CHS HDLP is a high-density lipoprotein of cholesterol; CHS LDLP is a low-density lipoprotein of cholesterol, TG is a triglyceride.

Methods for determining efficiency. The following indicators were taken into account in determining the effectiveness of the methods used:

- Dynamics of NO-system indicators;
- Dynamics of IL-6, TNF-α S-reactive protein (SRP);
- Hemodynamic indicators;
- endothelial-dependent vasodilation (EDVD) shift and endothelial shift force.

The results of the study were statistically processed using the software package STATISTICA 6.0 and using the established statistical processing methods.

Results and their discussion. The greater proportion of patients involved in the study was women, 59%. Based on the analysis of data from the anamnesis of the disease, the mean age of the patients at the time of the first signs of CHD was 48.7 ± 13.8. With the onset of the first symptoms, the mean period before the diagnosis of CHD was 6.9 ± 1.6 months. In turn, patients developed pain in the

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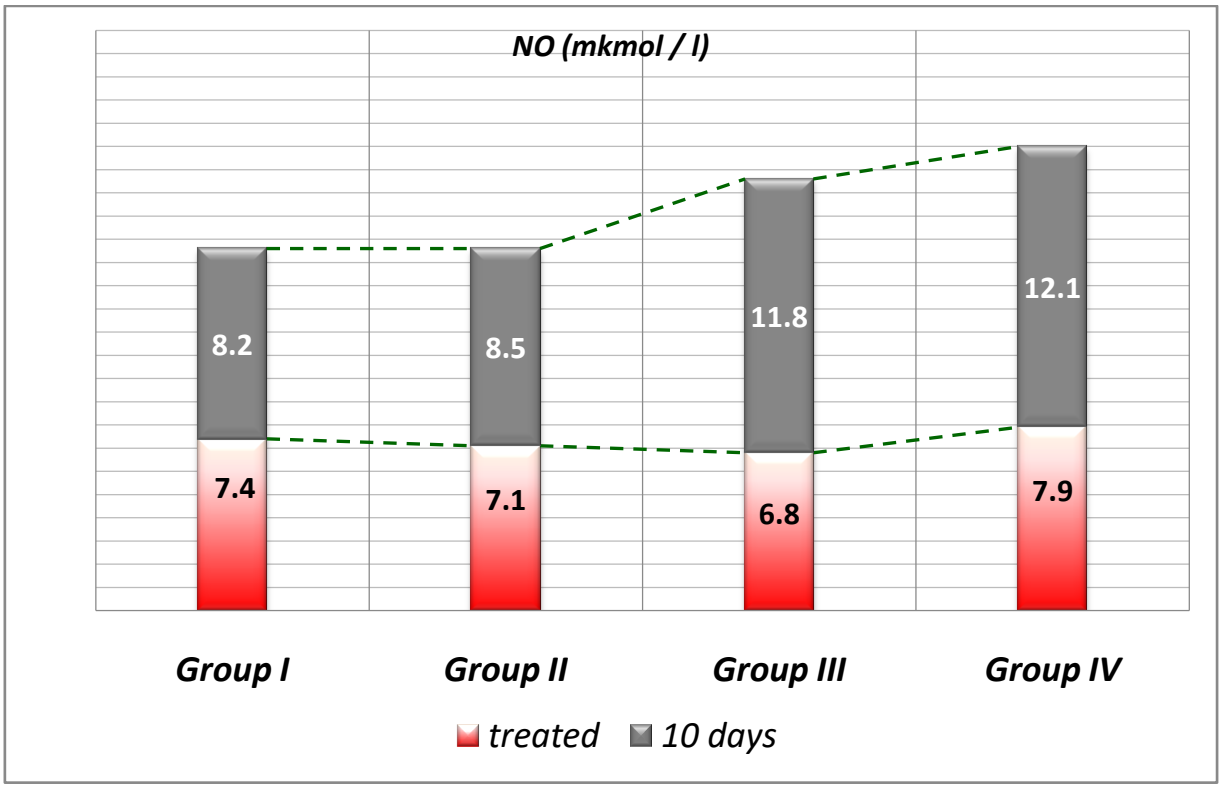
chest area and took an average of 2.7 ± 1.2 hours to be admitted to the hospital with ACS.

Symptoms other than ACS included general weakness (75%), irritability, sleep and attention disturbances (66%), restlessness, and fear (48%) in the patients involved in the study. In addition, grade I anemia was detected in 52% of patients.

According to the results of the examination of patients, an imbalance of the NO-system was observed in ACS. At the same time, a significant decrease in serum NO - 32.6% and eNOS - 36.5%, while iNOS - 45.5% and ONO2 - 48.2%. Hence, impairment of vascular endothelial activity was associated with NO-system imbalance. At the same time, ED is exacerbated by a sharp decrease in NO and eNOS due to the activation of iNOS expression and an increase in ONO2-concentration. In addition, an increase in the levels of cytokines IL 1b, IL 6, and TNF-α was observed on the basis of the immune-inflammatory response. It is known that based on the aggressiveness of TNF-α and IL-6, there is a possibility of vascular endothelial dysfunction [6, 11]. Today, despite the large number of studies devoted to the study of ED prognosis, the debate on the prognostic significance of a number of indicators in the literature continues. In other words, the role of ED is important in determining the severity and prognosis of the clinical course of the disease, as well as in the assessment of vascular remodeling, post-infarction remodeling of the myocardium, systolic and diastolic activity of the left ventricle.



Picture 1. Treatment-based NO dynamics.

The results of studying the dynamics of the above parameters in the blood serum of patients, depending on the method of treatment used, show that clinical

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correction of the disease and its stability can be achieved by adjusting their amount. The results of the study of endothelial activity showed that between the main and control groups there were significant differences in relation to the use of ACC. Figure 1 shows that in groups III and IV the amount of NO increased by the end of 10 days on the basis of a convincing (r <0.05) approach, while in control groups I and II there was a tendency to a statistically insignificant increase (r> 0.05), what happened.

Table 2

Dynamics of indicators of vascular endothelial activity on the basis of treatment in ACS

Indicators		**Group I** (n=25)	**Group II** (n=25)	**GroupIII** (n=25)	**Group IV** (n=25)
eNOS, (mkol/ dq/l)	*treated*	14,2±2,1	14,7±1,9	13,1±1,3	12,7±1,4
	10 days	16,4±0,9	17,1±3,2	19,3±1,1*	20,2±2,2**
iNOS, (mkol/ dq/l)	*treated*	0,49±0,2	0,51±0,3	0,48±0,1	0,5±0,2
	10 days	0,43±0,4	0,48±0,4	0,38±0,1	0,31±0,1*
ONO_2^-, (mkol/l)	*treated*	0,19±0,03	0,18±0,05	0,20±0,02	0,21±0,02
	10 days	0,17±0,02	0,14±0,02*	0,16±0,01*	0,13±0,01**

Note: confidence level * r <0.05, * r <0.01 relative to pre-processing values.

It is known that the level of NO is regulated by eNOS. In turn, when eNOS decreases due to hypoxia and ischemia, iNOS comes to the fore as the main source of NO production in tissues. In addition, the presence of iNOS produces more NO than eNOS [13]. Therefore, NO has vasoconstrictor properties and not a vasodilator. In addition, when NO is overexposed, the processes leading to the formation of superoxide anion radical (O2-) are simultaneously intensified. Under these conditions, NO is synthesized with O2- to form the highly cytotoxic compound ONO2-. In turn, studying the dynamics of the vascular NO-system based on treatment, it was found that there are differences between the indicators of the groups. According to the results, a certain dynamics of eNOS was observed in all groups on the basis of treatment (table 2), but significantly more pronounced (r <0.05 and r <0.01, respectively) in patients of group III. and especially IV. In turn, the decrease in iNOS was reflected depending on the ACC. As can be seen from Table 2, in contrast to other groups, the accuracy (r <0.05) decreased in group IV. In addition, ONO2 is of particular importance for the reduction of endothelium-related vasodilation, as seen in Table 2, which revealed significant and significant changes in all groups except group I.

Thus, the use of BE + ACC and CA + ACC from the first hours after the detection of ACS in patients has a positive effect on improving endothelial function, i.e. plays an important role in correcting the observed NO imbalance.

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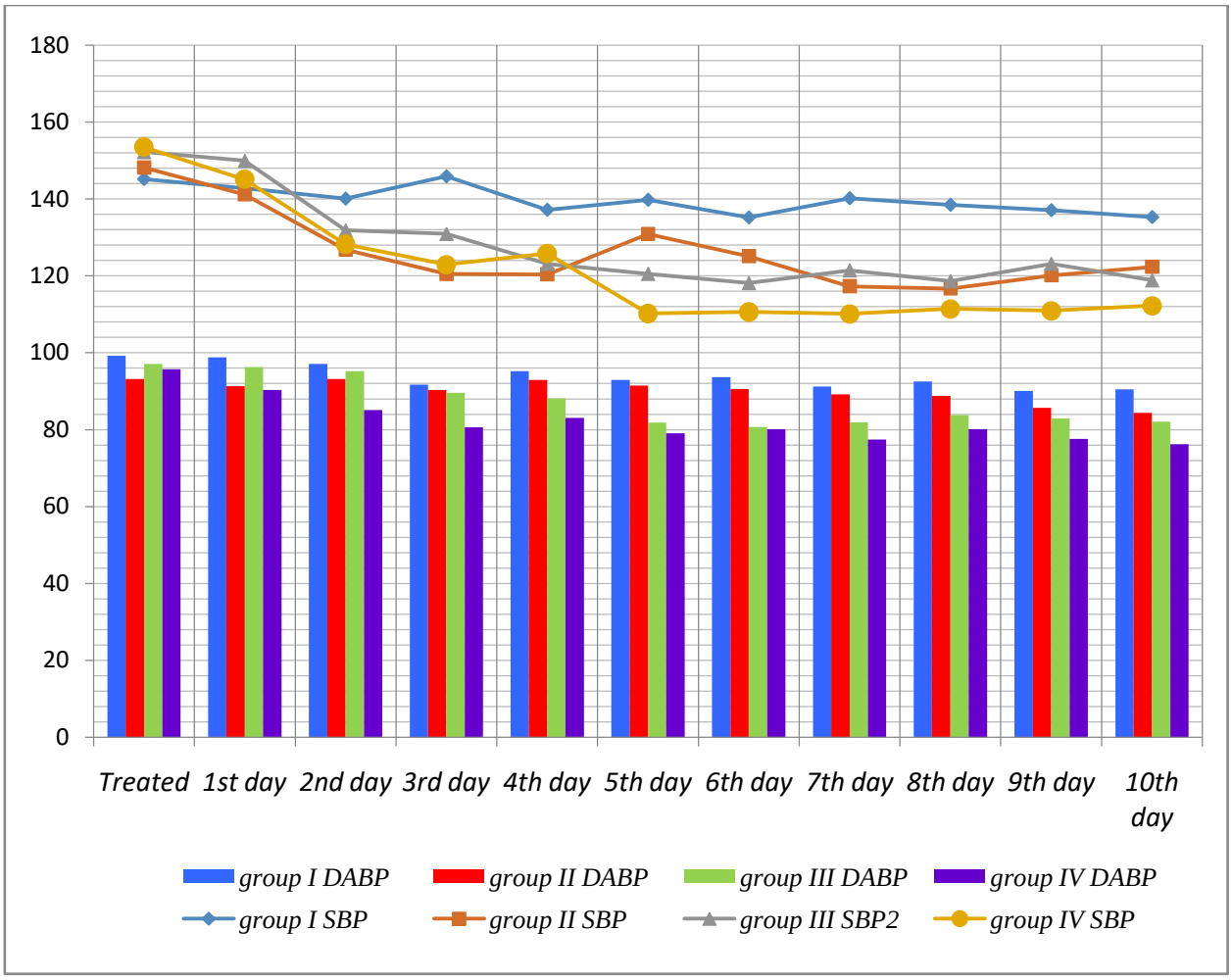


Picture 2. Dynamics of arterial blood pressure on the basis of treatment in ACS. SBP - systolic blood pressure, DABP- diastolic arterial blood pressure.

It is known that the stability of vasodilation is ensured on the basis of ED correction. Indeed, as can be seen from Figure 2, the dynamics of arterial blood pressure (ABP) at 10-day follow-up differed in specificity. On the basis of treatment in patients with ACS involved in the study, SBP / DABP in group I ranged from 145.2 ± 15.3 / 99.2 ± 7.8 to 135.3 ± 13.9 / 90.5 ± 5.3 (r> 0, 05); In group II from 148.2 ± 17 .8 / 93.2 ± 4.8 to 122.3 ± 10.1 / 84.4 ± 4.4 (r> 0.05); In group III, 152.4 ± 11.3 / 97.1 ± 5.1 to 118.8 ± 9.8 / 82.1 ± 3.9, (r <0.05); In group IV, 153.5 ± 11.2 / 95.7 ± 6.1 to 112.2 ± 9.8 / 76.2 ± 4.3 (r <0.05) mm. varied in mercury predominance. Thus, when using ACC in addition to 10 days of standard treatment, the SBP in group III increased by 22.04% (r <0.05), DABP by 15.4%, and in group IV by SAQB by 26.9%, DABP by 20.4%. decreased.

According to the literature data, ACC lead to the restoration of the NO balance by suppressing the activated matrix metalloproteinase by inhibiting iNOS [12, 14]. Of course, in such a situation, the disappearance of inflammation caused by the response of the immune system leads to a change in the clinical picture due to its direct dependence on the process of damage or necrosis of the myocardium [17]. In turn, according to the results obtained, a certain shift in the dynamics of pre-inflammatory cytokines was observed in all groups of patients during

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5975 - 5985
Received 05 March 2021; Accepted 01 April 2021.

treatment. It is known from Table 3 that by the end of the 10th day of treatment, there was no difference in TNF-α and IL 1b between the groups, and a significant decrease in these values was found in all groups (r <0.05).

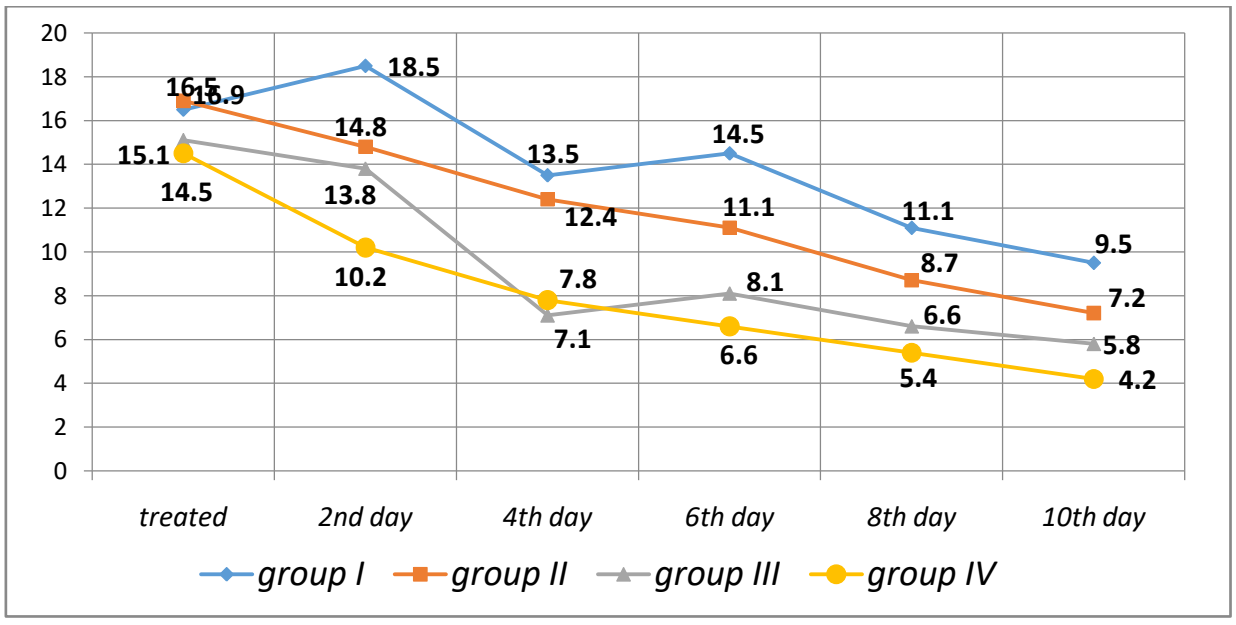
Table 3

Dynamics of treatment-based immune-inflammatory indicators in ACS

Indicators		Group I (n=25)	Group II (n=25)	Group III (n=25)	Group IV (n=25)
TNF-α (pg/ml)	*treated*	112,1±7,5	109,2±4,4	110,7±6,1	114,2±8,4
	10 days	88,1±9,9*	80,2±3,1*	107,1±3,5	71,2±3,8*
IL-6 (pg/ml)	*treated*	150,3±17,2	149,1±13,1	157,3±15,5	153,8±14,8
	10 days	140,2±19,4	109,6±12,5*	135,9±21,9	102,8±16,1*
IL-1β (pg/ml)	*treated*	114,3±11,5	105,4±10,1	110,2±9,6	112,8±12,2
	10 days	83,9±14,7*	73,4±9,6*	100,5±13,3	71,8±8,8*

Note: confidence level * r <0.05, * r <0.01, relative to pre-treatment values.

In addition, in the groups using BT + ACC and AC + ACC, there was a significant decrease in IL 6 (p <0.05), in contrast to groups I and II. In turn, the process of geometric remodeling of the heart due to an imbalance of nitric oxide (NO) products based on hypercytokinemia, SRP, which is an indicator of an inflammatory response due to the development of ischemia and myocardial necrosis, had a positive trend in all cases. groups, as shown in Figure 3. At the same time, although the 10-day follow-up for SRP was significantly lower than in all groups, control over the treatment outcome (group I 9.5 ± 1.2 mg / l; group II 7 , 2 ± 2.5 mg / L) and baseline (Group III 5.8 ± 1.3 mg / L; Group IV 4.2 ± 1.1 mg / L), a true difference was found between the groups (r <0 , 05).



Picture 3. Dynamics of S-reactive protein in OKS

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When evaluating the effectiveness of endothelial activity on the basis of treatment of ACS, the dynamics of reactive hyperemia pre- and post-test vascular diameter values were the cause of the shift in endothelial-dependent vasodilation (EDV). It was found that when ordering ACC along with BT and AT, EDV in groups III and IV increased by 39.5% (r <0.001) and 49.6% (r <0.001), respectively, at baseline 10 compared to baseline data. In groups I and II, treatment was characterized by an increase in EBVD of 23.4% (r <0.05) and 29.3% (r <0.05), respectively. In addition, positive dynamics of the endothelial shear force index (K) was observed in the treatment dynamics in all groups. At the same time, its value in groups III and IV increased by 30.6% (r <0.001) and 41.9% (r <0.01). In groups I and II, this figure was 16.7% (r> 0.05) and 29.1% (r <0.01).

Thus, the use of BD + ACC relative to BT resulted in a 16.1% increase in EBVD and CA + ACC compared to CA increased 20.3% in patients undergoing transformation from ACS to myocardial infarction. It was found that BD + ACC increased by 13.9% compared to BT and CA + ACC by 12.8% compared to CA.

Conclusion. Based on the results obtained, the use of BT + ACC and CA + ACC from the first hours in patients undergoing myocardial infarction has a positive effect on improving endothelial function by correcting NO-system imbalances. At the same time there is an improvement in the inflammatory process on the basis of hypercytokinemia, ie the cessation of IL-6 aggression. In addition, along with the improvement of hemodynamic parameters, it helps to restore endothelial activity.

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