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Evaluation of Long-Term Changes in the Levels of Inflammatory Factors during Postoperative Period in Patients with Acute Coronary Syndrome without ST-Segment Elevation Undergone Coronary Artery Bypass Surgery

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Abstract

Objective: One of the most effective and widely used methods of myocardial revascularization in patients with acute coronary syndromes is coronary artery bypass surgery (CABG). Chronic inflammation plays a significant role in the destabilization of atherosclerotic plaques in acute forms of ischemic heart disease and also in relapse of myocardial ischemia after myocardial revascularization. Ischemic myocardial injury is associated with activation of molecular and cellular inflammatory factors, the most important of which are cytokines, cell adhesion molecules (CAM) and leukocytes. Changing in the concentration of these agents during postoperative period reflects the intensity of the inflammatory and reparative processes in the myocardium. In this context, it is relevant to evaluate the long-term dynamics of inflammatory markers in the patients undergone coronary artery bypass grafting to predict the possible exacerbation of coronary heart disease.

Methods: The study involved 130 patients who underwent CABG surgery with acute coronary syndrome without ST-segment elevation. The comparison group consisted of 28 patients who suffered from stable coronary artery disease (average age 50.9 ± 1.2 years) with a history of MI, no earlier than 6 months prior to study entry. The levels of serum inflammatory markers (ICAM-1, TNF-α, IL-6, leukocytes) were measured before operation and 6.12, 24 and 48 months after CABG.

Results: The study showed that soluble intercellular adhesion molecule-1 (ICAM-1) and leukocyte levels in patients with non-ST elevation acute coronary syndrome gradually decreased during follow-up period in comparison with preoperative rates. sICAM-1 level increased up to 48 month and tended to preoperative value. There were no changes in tumor necrosis factor- alpha (TNF-α) and interleukin-6 (IL-6) levels during the whole follow-up period. TNF-α level in the patients with NSTE ACS before surgery have not differed from the level in the patients with stable ischemic heart disease (62.0 ± 9.8 pg/ml and 51.0 ± 6.8 pg/ml; p>0.05). TNF-α serum level has remained unchanged in the patients after CABG. Preoperative levels of IL-6 did not differ significantly among the patients with NSTE ACS and stable coronary artery disease (34.5 ± 3.6 pg/ml and 28.6 ±3.1 pg/ml; p>0.05). The IL-6 levels remained practically unchanged over time.

Conclusion: According to the results we can suggest, that further maintenance and development of the inflammatory process after CABG will contribute to the progression of coronary heart disease preserving the risk of exacerbation and reocclusion of coronary blood vessels.

Keywords: Acute coronary syndrome; Coronary bypass; Intercellular adhesion molecule-1; Proinflammatory cytokines; Leukocytes; Tumor necrosis factor - alpha; Interleukin-6

List of Abbreviations

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Surgery; CAM: Cell Adhesion Molecule; CHD: Coronary Heart Disease; ICAM: 1intercellular Adhesion Molecule-1; IL-6: Interleukin-6 NQMI: Non-Q Myocardial Infarction; NSTE ACS: Non-St Elevation Acute Coronary Syndrome; PCI : Percutaneous Coronary intervention; Sicam-1: Soluble Intracellular Adhesion Molecule-1; TNF-A: Tumor Tumor Necrosis Factor-Alpha; UA: Unstable Angina.

Introduction

Over the last few years a lot of attention has been paid to understand the reasons of clinical remanifestations of coronary artery disease after CABG. Chronic inflammation plays a significant role in the destabilization of atherosclerotic plaques in acute forms of ischemic heart disease and in relapse of myocardial ischemia after myocardial revascularization.

According to modern concepts, atherosclerotic coronary artery disease is equally associated with lipid metabolism disorders and inflammatory responses, the intensity of which increases with the development of acute coronary syndrome (ACS) [1,2]. Ischemic myocardial injury is associated with activation of molecular and cellular inflammatory factors, the most important of which are cytokines, cell adhesion molecules (CAM) and leukocytes. It is well

established that tissue infiltration by leukocytes is regulated by the CAM, which include intercellular adhesion molecule-1 (ICAM-1), which belongs to the immunoglobulin gene superfamily. The main function of ICAM-1 is participating in the processes of adhesion of white blood cells to the endothelium [3]. Adhesion and extravasation of leukocytes controlled by cytokines, especially tumor necrosis factor - alpha (TNF-α), which enhance the adhesive properties of endothelium, activate the expression of cell adhesion molecules, induce the formation of chemo attractive agents etc. Under the influence of TNF-α, endothelial cells and leukocytes induce expression of not only the ICAM, but also the production of interleukin-6 (IL-6), involved in the regulation of a further inflammatory reactions cascade [4,5]. According to the results of clinical studies it is shown that the serum level of TNF-α and IL-6 was significantly higher in patients with ACS than in patients with stable angina and in healthy individuals [6,7]. There is also evidence of the correlation between the levels of proinflammatory cytokines and severity of atherosclerotic coronary lesions, clinical variants of CHD and its prognosis [8].

Oxidative Stress

There are two types of invasive procedures in patients with non-ST-segment elevation acute coronary syndrome (NSTE ACS): percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG). Many studies, conducting analysis of PCI and CABG, demonstrate the advantage of the latter in the conservation of the positive effect of surgery, especially in patients at high risk [9]. The clinical need to predict long-term outcomes of CABG in acute forms of coronary heart disease is obvious. Timely detection of patients with high risk of recurrence of ischemia after CABG allows conducting optimal drug and non-drug prevention of complications. Because of the integral role of inflammation in atherogenesis, it is important to study the dynamics of inflammatory markers after surgical revascularization in patients with NSTE ACS and their relationship with clinical features of coronary artery disease in the postoperative period.

Methodology

To evaluate the dynamics of inflammatory markers after surgical revascularization in patients with NSTE ACS.

Materials and Methods

The study involved 130 patients who underwent CABG surgery with acute coronary syndrome without ST-segment elevation (NSTE ACS): 106 (81.5%) males and 24 (18.5%) women; the average age was 58.4 ± 0.8 years (range from 33 to 79 years); 37 of them (28.5%) were patients who had a myocardial infarction without Q-wave (NQMI), and 93 (71.5%) patients - with unstable angina (UA) (Table 1).

The diagnosis of NSTE ACS was based on the clinical picture of the disease, the presence of biochemical markers of myocardial damage (troponin-I, MB fraction of creatine phosphokinase), electrocardiography (ECG) and echocardiography (EchoCG). All patients with NSTE ACS received comprehensive drug therapy including anticoagulants (heparin), antiplatelet agents (aspirin), β-adrenergic blocking agents, nitrates, statins. The maximum period of follow-up of patients after CABG was 48 months.

The comparison group consisted of 28 patients who suffered from stable coronary artery disease (average age 50.9 ± 1.2 years) with a history of MI, no earlier than 6 months prior to study entry.

The levels of serum inflammatory markers (ICAM-1, TNF-α, IL-6, leukocytes) were measured before operation and 6, 12, 24 and 48 months after CABG. Determination of soluble intracellular adhesion molecule (sICAM-1) concentration was performed by ELISA using a test system, manufactured by DRG Instruments GmbH (Germany). The results are expressed in nanograms per milliliter (ng/ml). Immunoassay method was used to measure the level of IL-6 and TNFα in serum using a test system "Protein contour" (St. Petersburg). Results are expressed in picogram per milliliter (pg/ml).

Risk factors	Stable coronary artery disease (n=28; 100%)	Unstable angina (n=93; 100%)	Non-Q miocardial infarction (n=37; 100%)
Overweight (BMI > 24.9 kg/m2)	28 (100%)	52 (55.9%)	22 (59.4%)
Smoking	15 (53.6%)	28 (30.1 %)	15 (40.5%)
Hypertension	13 (46.4%)	75 (80.6%)	33 (89.2%)
Family history of CHD	5 (17.9%)	62 (66.7%)	23 (62.2%)
Lipid metabolism disorders	28 (100%)	17 (18.3%)	15 (40.5%)
(TC > 5.0 mmol/l; LDL ≥ 1.2 mmol/l)			

Table 1: Risk factors in patients with different types of coronary heart disease

Results

Analysis of the CABG results showed that during 48 months of observation there were no cases of death, proving the good effect of surgical treatment. In our study the evaluation of pro-inflammatory markers levels in patients with different types of the disease showed that in the group of patients with NSTE ACS before surgery there were higher mean values of sICAM-1 with respect to patients with stable coronary artery disease (680 ± 40 ng/ml and 580 ± 30 ng/ml, $p<0.05$). A study of the sICAM-1 in the dynamics after CABG showed a significant decrease of the molecule level during 24 months of observation; however, after 48 months, the concentration of sICAM-1 in serum reached preoperative levels (Table 2).

The average number of leukocytes in peripheral blood in patients with stable coronary artery disease (5.6 ± 0.3 × 109/L) was significantly lower than in group with NSTE ACS before myocardial revascularization (7.9 ± 0.2 × 109 / L, $p <0.001$). There was significant decreasing in white blood cell amount after performing CABG with relation to preoperative values at all stages of follow-up period (Table 1).

The study showed that the level of TNF-α did not differ significantly between group of patients with NSTE ACS before surgery and patients with stable coronary artery disease (62.0 ± 9.8 pg / ml and 51.0 ± 6.8 pg/ml; $p> 0.05$). After CABG there was no essential dynamics of TNF- α concentration in the blood serum (Table 2).

Similar changes were also observed for IL-6 concentration, which didn't show significantly difference between two groups of patients

(34.5 ± 3.6 pg/ml and 28.6 ± 3.1 pg/ml ; p> 0.05). With the passage of time after CABG (During follow-up period) level of IL-6 was changed slightly (Table 2).

Discussion

It is found that myocardial revascularization does not lead to complete cure of patients, because the risk of atherosclerosis in native coronary arteries and sites of anastomosis still remains. It is known that inflammatory process plays an important role in CHD initiation and progression [10].

According to this data, it can be assumed that the decrease in concentration of sICAM-1 right after CABG is connected with coronary blood flow recovery.

With increasing time after CABG, elevation of the levels of this adhesion molecule does not exclude the activation process of atherogenesis, because, as shown, the level of sICAM-1 in the blood stream reflects the activity of an inflammatory response in the atherosclerotic arteries [11]. Significant reduction in the number of leukocytes during postoperative period may indicates decreasing the intensity of the inflammatory process.

	Reference group	NSTE ACS Before CABG	Time after CABG (months)			
	(Stable CAD)		6	12	24	48
ICAM-1 ng/ml	580 ± 30	680 ± 40	535 ± 524.9**	570.3 ± 27.7*	584.4 ± 37.6	644.7 ± 21.7
TNF-α pg/ml	51 ± 6.8	62 ± 9.8	60.8 ±6.8	63.2 ± 4.7	63.5 ± 5.9	61.8 ± 5.9
IL-6, pg/ml	28.6 ± 3.1	34.5 ± 3.6	35.1 ± 5	34.5 ± 4.1	33.9 ± 6.2	35.5 ± 6.0
Leukocytes ×109/l	5.6 ± 0.3	7. 9 ± 0.2	6. 3 ± 0.2**	6.4 ± 0.4**	6.3 ± 0.4**	6.5 ± 0.3**

Table 2: Dynamics of inflammatory factors in patients with acute coronary syndrome without ST- segment elevation during follow-up period after coronary artery bypass surgery compared with preoperative levels. *P<0.05 compared with the value in group of NSTE ACS before CABG **P<0.01 compared with the value in group of NSTE ACS before CABG

Correlation analysis between the studied markers of inflammation revealed direct positive relationship between the content of the soluble form of ICAM-1 and the number of leukocytes in peripheral blood (r= 0.18; p <0.05). It is found, that during ischemic myocardial damage the expression of β_2-integrins (CD11/CD18) on the surface of leukocytes is increased, as well as P- selectin and ICAM-1 - on the coronary vascular endothelium. It is assumed that the level of soluble form of ICAM-1 in the systemic circulation reflects the intensity of endothelial- leukocyte interaction [7]. Knowledge of the adhesion and migration mechanisms of leukocytes may be important in the development of new approaches to the treatment of coronary artery disease. Thus, experimental works have shown that the use of antibodies to integrins CD11 / CD18, P-selectins and ICAM led to inhibition of postischemic leukocyte adhesion to endothelium and thereby reducing inflammation [13].

Many aspects of endothelial-leukocyte interaction are controlled by cytokines. The important role of TNF-α and IL-6 in the development of atherosclerosis is based on their diverse effects on differentiation and proliferation of various cells, as well as participation in the mechanisms of hemostasis, angiogenesis and immune-inflammatory reactions [14].

No significant differences in levels of TNF-α and IL-6 between groups of patients with ACS and ST BP stable course of the disease may be due to the fact that perhaps, in our study, these markers do not show the intensity of the inflammatory process. However, elevated levels of these markers in groups with stable angina and NSTE ACS, as well as their lack of dynamics in the postoperative period is likely to reflect the presence of an inflammatory process in the studied patients. Also ambiguity of the results needs further examination.

Conclusion

Results of the study showed that in patients with NSTE ACS after CABG there was reduction of soluble form of ICAM-1 and leukocytes within 6-12 months compared with the preoperative values. By the end of the study (48 months) the level of sICAM-1 increased and approached the preoperative value. At all stages of investigating the dynamics of the content of TNF-α and IL-6 were not insignificant. Such dynamics of proinflammatory cytokines reflects a maintenance of chronic inflammation after presenting CABG in patients with coronary heart disease.

According to the results of our study we can suggests that further development of the inflammatory process will contribute to the progression of coronary heart disease with the risk of exacerbation of the inflammatory process resulting in reocclusion of coronary blood vessels.

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