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Potential Anti-Inflammatory Treatment of Ischemic Heart Disease

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ABSTRACT

Introduction: Ischemic heart disease (IHD) is clinical manifestation of chronic inflammatory progressive pathological process of atherosclerosis in coronary arteries. IHD is the leading cause of morbidity and mortality in the world. The question is whether it is possible to improve and direct the therapeutic treatment of IHD patients in the treatment of the inflammatory process in the atherosclerotic leasions. Material and Methods: A prospective, comparative, analytica,clinically applicable, open-type study was performed. The study was conducted on 80 subjects with controlled biohumoral markers: troponin, CK, CK MB, BNP; markers of atherogenesis: LDL and homocystein; inflammatory markers: CRP, amyloid, cytokines IL-2, IL-6,TNF-alpha. The experimental group of 38 respondents had in addition to the conventional IHD treatment with: ampicillin (which included organosulfur compounds), cyancobalamin, vitamin B complex (B1, B2 and B6) and folacin. A control group of 42 respondents did not have this additional treatment. Results: Major adverse cardic events (MACE) such as postinfarctic angina pectoris and repeated infarction, need for surgical interventions of myocardial revascularization, signs of cardiac insufficiency and death were observed during the one-year period. There was no correlation between the IL-2, IL-6 and TNF-alpha, as well as CK, CKMB and troponin and MACE in one-year follow-up. There was a strong positive correlation between MACE and CRP (p = 0,0002) and amyloid (p = 0,0005) as inflamatory markers; a strong positive correlation between MACE and homocysteine as an atherogenic marker (p = 0,0002, and amoderate positive correlation between MACE and BNP (p = 0.0403) as ischemic marker and marker of cardiac insufficiency. The echocardiographically monitored systolic function showed a moderate difference in the groups with average higher values in the experimantal group (p = 0.0282). Conclusion: The applied treatment exhibited a moderate positive effect on the systolic function of LV and significantly reduced the MACE in the work compared to the control group (p <0.0001), and demonstrated a potential anti-inflammatory effect.

Keywords: ischemic heart disease, marker, ampicillin, vitamin B complex, MACE.

1. INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality in the world, with 29% of total annual mortality. It is estimated that by 2030, 23.6 million people will die annually of heart disease, or every two seconds in the world will cause a death due to cardiovascular disease (1). Cardiovascular diseases are the cause of death in our country, especially in younger age population, according to data from the FBiH Public Health Institute (2). Ischemic heart disease (IHD) in cardiovascular disease amount to 42%. Myocardial infarction is the leading cause of mortality in Western Europe with an intrahospital mortality rate of 6-13%, or 30%-40% when extrahosital mortality is considered (3). The pathophysiological basis of cardiovascular

disease is atherosclerosis as an inflammatory disease in which immune mechanisms interact with metabolic risk factors in the occurrence, propagation and activation of lesions in the arterial wall. Atherosclerosis ends with occlusive disease of coronary, carotid, cerebral and peripheral arteries. Atherogenic factors in the emergence and progression of atherosclerosis are: elevated levels of LDL cholesterol, elevated homocysteine, smoking, hypertension, diabetes, viral and bacterial infections, immune complexes and insufficiently defined toxins. All stages of atherogenesis are morphological and functional changes of the endothelium known as endothelial dysfunction (ED). The essential factor of atherogenesis and ED is homocysteine which causes smooth muscle cell hyperplasia, decreases NO secretion and oxidizes LDL, and acts atherogenic and thrombogenic (4). Ultimately ED causes rupture of atherosclerotic plaque, formation of fever, ulceration and thrombosis. The clini-

cal manifestation of this process on the coronary arteries is IHD. After occlusion of the coronary artery, myocyte necrosis occurs, and intracellular macromolecules diffuse into interstitial and microvascular structures in the area of myocardial infarction as serum cardiac markers. Significant sensitized and specific myocardial necrosis markers are: creatine kinase (CK), its isoenzyme CK MB, troponin, and a new proven ischemic marker and marker of cardiac insufficiency–brain natriuretic peptide (BNP). Increasing the level of circulatory inflammatory markers correlates with the prognosis of acute coronary syndrome (ACS), regardless of the degree of ischemia or the extent of atherosclerotic changes. Such inflammatory markers are: CRP, serum amyloid, IL-6, TNF-α, etc. Thus, it can be assumed that inflammation is one of the possible goals of IHD treatment. The leading predictor of inflammatory marker i CRP. Synthesis and CRP production (controlled by predominantly IL-6) begins very rapidly in acute myocardial infarction (AMI), increases by 5 mg/l for 6 hours and reaches maximum within 48 h. Under the influence of IL-6 and TNF-α very rapidly in AMI, the synthesis of another inflammatory marker amyloid begins (5). During AMI serum amyloid starts to grow within 24 hours and its peak value reaches three days after the onset of pain 2000 times the third day by AMI (6). The gold standard in IHD diagnosis and coronary syndrome is coronarography. Coronary plaques with luminescent stenosis of up to 50% usually do not fall under percutaneous coronary treatment, but unfortunately these inflammatory plaques are in the large number of cases caused by AMI. In coronary heart disease, it was found that up to 70% of people with AMI plaque of less than 50% had the rupture. The so-called unstable, lipid-rich plaques are most suitable for modification, reduction of lipid content and degree of inflammation, and therefore, theoretical, and possible regression. Treatment of inflammation in the coronary artery would achieve a better cost-benefit in IHD treatment, the costs of diagnosis and treatment, absenteeism, disability, and mortality of the patients would be reduced. The question arises as to whether additional antibiotic therapy due to the potential involvement of plaque-afflicted microbes and vitamin B complex therapy due to the positive effect on homocysteine metabolism may influence the aterogenesis and inflammation of atherosclerotic plaques of coronary arteries and obtain benefit in the treatment of IHD.

Goals of the investigation are:

- Determine the plasma levels of cytokines (IL-2, IL-6, TNF-α), CRP and amyloid as inflammatory markers in the investigated groups and determine the plasma levels of homocysteine and LDL, CK, CK- troponin, and BNP.
- Determine the correlation between the value of the examined markers and the systolic function of LV.
- Apply an additional therapeutic treatment with ampicillin, cyancobalamin, folacin and vitamin B complexes (B1, B2, B6) in subjects.
- Determine the possible relationship between the values of the examined markers and the applied therapeutic treatment with MACE in IHD.

2. MATERIAL AND METHODS

A prospective, comparative, analytical, clinically applicable open type study was performed, which included 80 subjects, of both genders, divided into the experimental (38) and control group (42). The study was conducted on the basis of a common approach to a patient including anamnesis, physical examination, ECG, echocardiography and laboratory tests at the Clinic for Heart, Blood Vessel and Rheumatic Diseases, in Intensive Coronary Unit. Blood samples were analyzed by the Central Laboratory for Clinical Biochemistry and Immunology Institute CCUS. The research was conducted in 2008. Inclusion criteria were: unstable angina pectoris, vasospastic angina pectoris, acute myocardial infarction without ST elevation (NSTEMI), acute myocardial infarction with ST elevation (STEMI). The non-inclusion criteria were: previous cardiac valve disease, advanced cardiomyopathy, associated renal insufficiency, acute infection, seropositive rheumatic diseases, malignancy, pregnancy, and allergy to penicillin and vitamin B complex. The exclusion criteria were allergies during the research and the patient's non-cooperation. STEMI patients were initially treated with fibrinolytic therapy-streptokinase, and all patients were treated with enoxaparin in intrahospital treatment and under the therapy of statin, aspirin, ACE inhibitors, beta blockers and nitro preperations. The experimental group had in th. addition ampicillin 2 gr. daily for 7 days, and vitamin B complex (Polibevit: B1 4.0 mg, B2 5.0 mg, B6 2 mg) 3 x daily with cyancobalamin 500 μg 2 daily and folic acid 5 mg 1 x daily perorally, 1 month. Laboratory control of blood on cardiac biohumoral markers: troponin, CK, CK MB, BNP; and inflammatory markers: CRP, amyloid, cytokine IL-2, IL-6, TNF-α; with homocysteine and LDL as atherogenic markers. On the tenth day of hospitalization, laboratory blood tests on the same markers and echocardiography were performed. One year later, a control echocardiographic examination was performed and adverse cardiovascular events were followed: postinfarctic angina pectoris and myocardial reinfarction, need for surgical revascularization, heart failure (NYHA II-IV), and death outcome. IL-2, IL-6 and TNF-α were determined by Elisa assays that are enzymatically mediated immunoassays for quantitative determination of human cytokines in serum. Concentration of CRP was determined by laser nefelometry (BM II analyzer), with a reference value of 0-5 mg/L. Determination of the serum amyloid was performed by a non-ephemeral method. The reference serum amyloid value determined by this method is up to 6.4 mg/L. Homocysteine in serum was determined from blood samples in gel tubes that were transported on ice to the Central Laboratory. The concentration of homocysteine is quantitatively determined by the method of fluorescence polarization immunoassays on AxSYM system, with a normal value of 5-15 μmol/L, and preferably 9-10 μmol/L. LDL concentration is determined according to the Friedvald formula:

Demographic characteristics of respondents	Experimental group N=38	Control group N=42	P
Age			
Mean (SD)	55.42 (6.98)	55.71 (9.60)	P = 0.8773
Median	54	56	
Rank	43 – 72	33 – 78	
Gender			
Female (%)	13 (34%)	13 (31%)	P = 0.9624
Male (%)	25 (66%)	29 (69%)	

Table 1. Basic demographic characteristics of respondents.

Marker	Rho (rank correlation)	N	p
IL-2	Rho=0.0460	80	p=0.7778
IL-6	Rho=0.234	80	p=0.1463
TNF-α	Rho=0.0447	80	p=0.694
CRP	Rho=0.407	80	p=0.0002
Amyloid	Rho=0.381	80	p=0.0005
Homocysteine	Rho=0.403	80	p=0.0002
LDL	Rho=0.102	80	p=0.3659
CK	Rho=0.0515	80	p=0.6500
CK MB	Rho=0.0784	80	p=0.4896
Troponin I	Rho=0.145	80	p=0.1982
BNP	Rho=0.230	80	p=0.0403

Table 2. The correlation of the tested markers between the experimental and control groups.

	Experimental group EF (%)	Control group EF (%)
Sample	38	42
Mean	51.5000	48.1905
95% CI of mean	49.2308 to 53.7692	46.2157 to 50.1652
Variance	47.6622	40.1580
SD	6.9038	6.3370
SEM	1.1199	0.9778

Table 3. Statistical analysis of heart ECHO for LVEF–control measurement

LDLC = UH–HDLC–VLDLC, and the concentration of total cholesterol, triglyceride and HDL cholesterol for its conversion is determined by the enzymatic, colorimetric method on the Dade Dimension AR analyzer. Troponin I concentration was determined quantitatively by hemiluminescence immunoassay with STAT Troponin-I reagent Abbot architect system. The upper reference value of troponin concentration by this method is 0.4 ng / mL. CK was determined by quantitative kinetic UV method, while CK-MB activity was determined by quantitative immunoinhibitory kinetic UV test. For laboratory measurement of BNP, a microparticulate enzyme immunoassase for quantitative determination of human BNP in EDTA plasma was used, on the AXSYM system. Transthoracic echocardiography was performed on the TOSHIBA POWER VISION 7000, and systolic function LV was estimated through ejection fraction (EF) by

Simpson method. Statistical analysis was performed using MedCalc for Windows version 11.2.0.0. Mann Whitney's test and Spearman's coefficient rank correlation ρ (rho) were applied. The correlations between the

Groups	Major adverse cardiac events PA (%)	RIM(%)	SRM (%)	CI (%)	D (%)	Total N
Experimental	6 16%	1 2.5%	5 13%	3 8%	1 2.5%	38
Total			16 42%			
Control	13 31%	5 12%	8 19%	10 42%	1 2.0%	42
Total			37 88%			

Table 4. Statistical analysis of the relationship of probable linkage (ODS)

	Codes X		
Codes Y	Control	Experimental	
No UCOE*	5	22	27 (33.7%)
UCOE	37	16	53 (66.2%)
	42 (52.5%)	38(47.5%)	80
Chi-square (χ2)		16.871	
DF		1	
Significance level		P < 0.0001	
Contingency coefficient		0.417	

Table 5. Chi-square test for evaluation of treatment outcome. (MACE*-unfavorable cardiac outcome event)

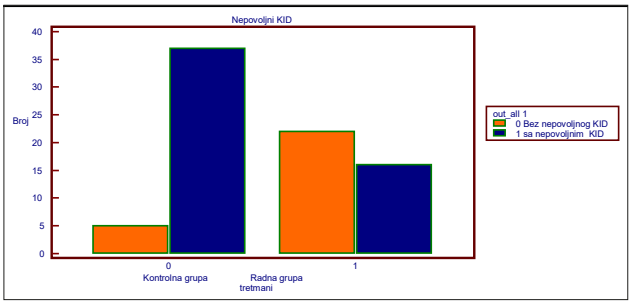

Figure 1. Chart based on MACE frequency in both groups.

outcomes were calculated using the chi-square test. Values for which p<0.05 were accepted as statistically significant.

3. RESULTS

Results are presented by tables and graphs. There was no statistically significant difference in age and gender between the analyzed groups. Of the tested CRP markers, amyloid, homocysteine and BNP were in positive correlation with MACE. In the experimental group with the applied additional treatment there was a significant decrease in these markers and significantly less frequent MACE. Student's T-test for independent samples compared the LVEF findings. There was a significant difference in the results between the experimental (M = 51.5,000, SD = 6.9038) compared to the control (M = 48.1905, SD = 6.3370) group t (78) = -2.236, p = 0.0282 (two-sided). The difference between mean values per group (mean difference = -3.3095, 95%, CI: -6.2566 to -0.3624) was moderate. MACE by groups (PA–post-infarctic angina, RMI–Repeated myocardial infarction, SRM–surgical myocardial revascularization, CI–cardiac insufficiency, D–death)

OR = ad / bc = 16 * 5/37 * 22 = 80/814 = 0.0983

In the experimental group, MACE was observed in 16 subjects within 12 months and in the control group in 37 subjects.

There was no a statistically significant imbalance by age and gender groups tested in this research.

Since the tested markers CRP, amyloid, homocysteine and BNP were positively correlated to MACE by the reference. In the experimental group with the applied additional treatment was a significant drop in these markers and significantly less frequent adverse cardiac parent events.

Student t-test for independent samples were compared to the results of the LVEF at baseline. A significant difference in the results between the experimental (M = 51.5000, SD = 6.9038) compared to control (M = 48.1905, SD = 6.3370) group t (78) = -2.236, p = 0 , 0282 (both sides). The difference between means of the groups (mean difference = -3.3095, 95% CI: -6.2566 to -0.3624) was moderate.

Major adverse cardiac events * (PA–postinfarction angina, RMI–reinfarction, SR–surgical revascularization, SI–cardiac insufficiency, D- death)

OR = ad / bc = 16 * 5/37 * 22 = 80/814 = 0.0983 in the experimental group in 16 followed were recorded by major adverse cardiac events root (Nkido) for 12 months in the control group 37 subjects. Based on the result obtained by the OR these results OR = 0.0983, 95% CI = 0.0316 to 0.3056, z = 4.008, p = 0.0001.

Chi-square test showed a significant difference between the applied treatment and outcome. p <0.0001, r = 0.417. Chart for Chi-square test based on the frequency of MACE originating in both groups. MACE are significantly more frequent in the control compared to a experimental group of respondents.

4. DISCUSSION

It is known that 50% of patients with IHD have no known risk factors. It is assumed that in such cases inflammatory reactions have a significant role in the pathogenesis of ischemic heart disease (7). The associationof IHD and some infectious agents such as Chlamydia pneumoniae, Helicobacter pylori, Herpes Simplex Virus, CytoMegaloVirus and Hepatitis A, respiratory tract infections and dental infections are mentioned in earlier epidemiological studies (8, 9). The Helsinki Heart Study suggests that chronic infection with Chlamydia pneumoniae can be a significant risk factor for IHD (10). The presence of Helicobacter pylori DNA was demonstrated in the aortic wall in atherosclerotic plaques of most patients with IHD. Jaffarzadeh et al.

Studied anti-Helicobacter pylori IgG seroprevalence and anti-Helicobacter pylori antibody titre titer, and finds that it is significantly higher in IHD patients than in the control group (11). In the CLARIFY study of 148 subjects with unstable angina and non-Q MI, treated with 500 mg of clarithromycin daily 3 months, AMI and heart failure were observed, and better outcome was observed in placebo vs. p = 0.015. (12) The AZACS study with 1450 subjects in the 5-day period did not demonstrate the benefit of such short-term antibiotic therapy (13). In 12 studies vitamin B12 in the 5-year period (16), while NORVIT study lasting 40 months showed a decrease in homocysteine, but a paradoxical increase in vascular risk in patients with combined folacin and vitamin B6 therapy (17). The SEARCH study, conducted on 12,000 subjects divided into two groups according to the dose of statin simvastatin (80mg: 20mg + both groups of folic acid 2mg and B12 1mg, 6.7 years), had more frequents myopathy (18). In most studies conducted with antibiotics, macrolide antibiotics were used, ampicillin was used in this paper for its good tolerability, broad spectrum of activity, and the cost of the cost. Ampicillin is a molecular formula C16H19N3O4S, and belongs to organosulfuron compounds including alicycline, cysteine, methionine and alpha lipoic acid. More recently, the current theory of sulphate deficiency is the cause of atherosclerosis, that is, of the deficiency of cholesterol sulphate (19,20). There is growing discussion about the positive role of sulphates in metabolism and prevention of oxidative stress, and their cardioprotective action. It is possible that the choice of ampicillin in the work, not some macrolide antibiotics, in combination with folacin, cyancobalamin and vitamin B6, which are necessary co-factors in the metabolism of homocysteine, was the key to success and more favorable outcome in the treatment of the study group. Namely, the American Food and Drug Administration (FDA) issued a 2013 warning that the macrolide antibiotic azithromycin could potentially cause fatal heart rhythm disorders due to the risk of prolongation of the QT interval (22, 23, 24), although it was apparent that its proaritmogenic effect was lower in compared to other macrolides (25). In the 2014 meta-analysis, the use of azithromycin was analyzed for the purpose of secondary prevention of MACEs and there was no proven benefit of its use compared to placebo (26). Ampicillin has been used for the prevention of endocarditis in valve patients for years and, as far as it is known, there have been no warnings about the detriment of its effect on cardiac patients. In our research, no respondent was excluded from the experimental group due to the intolerability of the treatment. Furthermore, no correlation or statistically significant correlation between the value of the investigated cytokines: IL-2, IL-6 and TNF-α, as well as LDL, CK, CKMB and troponin and MACE, was not demonstrated in oneyear follow-up. There was a strong positive correlation between MACE and CRP (p = 0,0002), amyloid (p = 0,0005), homocysteine (p = 0,0002), and moderate for BNP (p = 0,0403), so the applied treatment in the experimantal group led to a significant fall in their values, and these markers proved to be prognostic because the number of subjects in the experimental group was significantly lower in the MACE. The echocardiographically monitored systolic function, by measuring the EF LV method by Simpson, showed a moderate difference in the groups with average higher values in the experimantal group (p = 0.0282). The additional therapeutic treatment with ampicillin, vitamin B complex, folacin and cyancobalamin in the study team significantly reduced MACE and demonstrated potential antiatherogenic anti-inflammatory effects. The pro-

portion of patients with MACE was significantly lower in the working group, $\chi 2 = 16,871$, $p < 0,0001$, $K = 0,417$ (Yates' Correction for Continuity) was applied.

5. CONCLUSION

Examined additional treatment in IHD, with ampicillin and vitamin B complex, folacin and cyancobalamin showed potential anti-atherogenic and anti-inflammatory effects and statistically significantly reduced the risk of MACE. Such therapeutic treatment should be investigated on a large number of subjects and considered such a therapeutic approach to the prevention of adverse outcomes in ischemic heart disease.

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