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Dynamics of the Indicators of Low Dose Dobutamine Stress-Echocardiography under the Influence of High Doses of Atorvastatin in Patients with ST Elevation Myocardial Infarction

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Abstract

The aim of investigation: to study the effect of early administration high doses of atorvastatin in the acute period of STEMI on the indicators of low dose dobutamine stress-echocardiography and parameters of left ventricular remodeling. ***Material and Methods***: The study included 164 patients with STEMI All patients underwent myocardial revascularization (TLT or PCI) within the first 6 hours. The 1st group included 82 patients who received basic therapy (atorvastatin 20 mg), the 2nd group included 82 patients who took a loading dose of atorvastatin (at a dose of 80 mg per day). Low dose dobutamine stress-echocardiography was performed to detect myocardial stunning after stabilization of the patients condition on 4–6 days of the disease. In addition to general clinical and conventional laboratory research methods, on the 1st day and on the 10th day of treatment, the level of CPK MB, ESR, the number of blood leukocytes, and the level of fibrinogen (FN) were determined. ***Results:*** On the 10th day of therapy in patients of both groups, there was a significant increase in ESR (in the 1st group by 2.1 times, in the 2nd - by 1.6 times) and a decrease in the level of CRP (by 3 and 2.65 times, respectively) compared to the first day. The dynamics of these indicators reflects the regular processes of the course of AMI. A more significant change in these parameters was recorded in patients of the 2nd group who took atorvastatin at a dose of 80 mg. At the same time, on the 10th day of AMI, the number of peripheral blood leukocytes significantly decreased in them ($p<0.05$ when compared between groups). The number of dobutamine-responsive segments (segments with reversible dysfunction) in the group of patients treated with atorvastatin at a dose of 80 mg during myocardial reperfusion was significantly higher than in the control group ($p<0.05$). ***Conclusion:*** It was revealed that conducting of myocardium reperfusion in infarct-related coronary artery with simultaneous use of atorvastatin's high doses promoted the limitation of myocardial necrosis development, reducing ischemic and reperfusion injuries of myocardium and influenced on the formation of myocardial stunning zones which is a reversible disfunction. The use of atorvastatin in the dose of 80 mg/per day in the first hours after acute myocardial infarction development promotes the improvement of LV systolic indices, prevents the progressing of LV cavity postinfarction dilatation.

Keywords: statins, acute myocardial infarction, left ventricle remodeling, stunning.

INTRODUCTION

Intensive care for acute ST-segment elevation myocardial infarction (STEMI) involves the use of several multi-drugs. It should be noted that statins are well compatible with almost all groups of drugs widely used in cardiology practice: antithrombotic drugs, nitrates, β-blockers (β-AB), angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics, etc. Thus, under the influence of thrombolytic therapy (TLT) and percutaneous coronary interventions (PCI), myocardial blood supply is restored, ACE inhibitors reduce the formation of endothelin-1, normalize the impaired function of the endothelium, its ability to release nitric oxide, and improve the processes of postinfarction remodeling of the left ventricle (LV) [1, 9, 16]. β-AB, inhibiting the effects of the sympathetic nervous system, reduces the likelihood of damage to the endothelium of the vascular wall [6]. One of the most solid studies confirming the effectiveness of the combined use of revascularization and lipid-lowering therapy is the Swedish RISK-HIA registry, which included 22 thousand patients under the age of 80 years after large-focal MI, who underwent myocardial revascularization and early lipid-lowering therapy. As a result, it was found that standard therapy without early

restoration of blood flow and prescription of statins caused the maximum increase in 1-year mortality after myocardial infarction [4, 9, 13].

Revascularization and early initiation of statins reduced the one-year mortality risk by 34%. Among patients who were prescribed statins on the first day of MI, in-hospital mortality and the combined point (in-hospital mortality + reinfarctions) were significantly ($p = 0.05$) lower (1.7 and 3%, respectively) than in patients who did not have statins. used (respectively 8.2 and 12%). The frequency of complications associated with restenosis of the coronary artery during the hospital period of AMI in patients treated with statins after TLT was significantly lower [9, 13, 16, 18].

The CHAMP study (Cardiac Hospital Aterosclerosis Management Program) analyzed changes in mortality and morbidity with changes in the treatment tactics of patients with AMI in 1994-1995. compared to 1992-1993. The results showed that increasing the frequency of prescribing aspirin, β-blockers, ACE inhibitors, and statins reduced overall mortality, recurrent MI, heart failure, and hospitalizations [15]. The priority of a specific statin drug for the treatment of patients with AMI after TLT remains a subject of study.

Statins have different lipid-lowering activity - from moderate (fluvastatin, pravastatin) to very high (atorvastatin, rosuvastatin) [6, 15]. Atorvastatin is the first choice drug with a strong evidence base for improving cardiovascular prognosis in acute coronary syndromes (MIRACLE, PROVE-IT). To date, convincing information has been obtained on the benefits of the prospective use of rosuvastatin in large-scale studies on primary and secondary prevention of atherosclerosis [5, 14]. In clinical practice, however, simvastatin is widely used as the most cost-effective drug [6, 11, 12]. The studies clearly demonstrated a more favorable effect on the prognosis in acute coronary syndromes of the so-called aggressive statin therapy (80 mg) compared to less aggressive (40 mg) treatment. However, given the rather high cost of such treatment and the increase in side effects when using high-dose statins, for the secondary prevention of complications of AMI, a starting dose of 20 mg of simvastatin and 10 mg of atorvastatin with a subsequent increase to 40 mg is recommended. For AMI, treatment with statins, as recommended by the ACC/ANA (2004), should be given to virtually every patient, regardless of low-density lipoprotein cholesterol levels, for as long as possible. At the same time, it is desirable to reduce the cholesterol content to the target values [4, 6, 17]. Large international randomized trials have shown that statins are currently the only class of drugs that, when used early in patients with MI, reduces post-reperfusion damage, reduces overall and cardiovascular mortality, the risk of relapse and recurrent MI, stroke, the need for surgery for restoration of coronary blood flow (coronary bypass grafting and transluminal balloon coronary angioplasty). Although the effect of statins on myocardial stunning and the processes of post-infarction LV remodeling has not been fully studied, this was the prerequisite for this study [18].

The aim of investigation

To study the effect of early administration of high doses of atorvastatin in the acute period of STEMI on myocardial stunning and parameters of left ventricular remodeling.

MATERIAL AND METHODS

The study included 164 patients with STEMI who were in the cardiotherapeutic resuscitation department of the Republican Scientific Center for Emergency Medicine. All patients were hospitalized within the first 6 hours from the onset of the disease (mean time of admission was 4.3±0.1 h). The average age of patients was 55.8±0.6 years. All patients underwent myocardial revascularization (TLT or PCI) within the first 6 hours. The 1st group included 82 patients who received basic therapy (atorvastatin 20 mg), the 2nd group included 82 patients who took a loading dose of atorvastatin (at a dose of 80 mg per day), prescribed in the first 24 hours from the development of the disease, regardless of lipid profile of blood. The groups of patients were comparable in terms of initial clinical and anamnestic data and treatment regimens. In order to study intracardiac hemodynamics on the 1st day and 3 months after AMI, two-dimensional echocardiography was performed using the Siemens Sonoline Omnia and Philips Clear Vue 650 apparatus with the calculation of end-diastolic and end-systolic volume, ejection fraction (EF) of the left ventricle. Stress echocardiography with low doses of dobutamine was performed to detect myocardial stunning after stabilization of the patients' condition on days 4–6 of the disease. In addition to general clinical and conventional laboratory research methods, on the 1st day and on the 10th day of treatment, the level of CPK MB, ESR (by the Panchenkov unified micromethod), the number of blood leukocytes, and the level of fibrinogen (FN) were determined. For statistical analysis of the results, Microsoft Excel 2016 spreadsheets and the SPSS 11.0 statistical program on a personal computer were used. Significance of differences between the compared groups was determined using Student's t-test.

RESULTS

Initially, the parameters of the blood lipid spectrum did not differ in the patients of the two groups (Table 1). However, already on the 10th day of observation in patients of the 2nd group who received high doses of atorvastatin, a significant decrease in the level of total cholesterol was recorded from 5.83±0.17 to 4.63±0.13 mmol/l ($p<0.001$) and LDL-C from 3.56±0.17 to 2.37±0.15 mmol/l ($p<0.01$). In patients of

the 1st group, who took atorvastatin at a dose of 20 mg, the parameters of the blood lipid spectrum did not differ significantly from the baseline, although there was a tendency to decrease them. In patients of the 1st group, during 10 days of treatment, the level of total cholesterol decreased by only 4.8%, while in the 2nd group - by 21% ($p<0.001$), LDL cholesterol - by 14 and 32%, respectively ($p<0.01$). One of the main indicators that determine the hospital and long-term prognosis in patients with AMI is the mass of necrotic myocardium and the rate of formation of the necrosis zone [3]. There is a close relationship between the size of MI and the development of heart failure (HF), the occurrence of rhythm disturbances. During recanalization of an infarct-related coronary artery, reperfusion injury of the myocardium develops in the early stages of the disease, which leads to additional myocardial necrosis in the areas of ischemic damage. Therefore, in order to clarify the comparability of patient groups, as well as the possible effect of atorvastatin on reperfusion myocardial injury in the blood serum of patients with AMI, the activity of CPK-MB, which is a marker of the formation of myocardial necrosis, was determined. The magnitude of the peaks of CPK-MB activity in patients of both groups was 1802±44 and 1424±36 arb., respectively. units, which indicates the severity of myocardial damage in patients of the 1st group. In patients with STEMI of the 2nd group, early administration of atorvastatin at a dose of 80 mg/day more significantly protected the myocardium from additional reperfusion damage during revascularization. The effect of early administration of atorvastatin at a dose of 80 mg/day on the severity of systemic inflammation was assessed based on the study of systemic inflammation markers (ESR, FN) on days 1 and 10 of treatment. Initially, there were no differences in the level of the studied markers of systemic inflammation between the patients of the two groups (Table 1).

Table 1: The effect of atorvastatin on the level of inflammatory markers in patients with AMI on the 1st (numerator) and 10th (denominator) days

Index	1st group	2nd group
Leukocytes $x10^9$ /l	8,9±0,25 7,5±0,25	9,0±0,25 6,0±0,25*^
ESR, mm/h	9,08±0,8 19,0±0,8*	9,9±0,8 16±0,8*^
SRP, mg/dl	30±0,7 10±0,7*	26±0,7 7,8±0,7*
Fibrinogen, g/l	3,2±0,05 3,1±0,05	3,52±0,05 3,4±0,05

Note. *-$p<0.05$ - in comparison with the initial data; ^- $p<0.05$ - compared with the 1st group.

On the 10th day of therapy in patients of both groups, there was a significant increase in ESR (in the 1st group by 2.1 times, in the 2nd - by 1.6 times) and a decrease in the level of CRP (by 3 and 3.33 times, respectively).) compared to the first day. The dynamics of these indicators reflects the regular processes of the course of AMI. A more significant change in these parameters was recorded in patients of the 2nd group who took atorvastatin at a dose of 80 mg. At the same time, on the 10th day of AMI, the number of peripheral blood leukocytes significantly decreased in them ($p<0.05$ when compared between groups). It is known that in AMI, proinflammatory cytokines initiate and maintain inflammation processes [8], in particular, they stimulate the migration of leukocytes to the affected area. In turn, activated leukocytes infiltrate the myocardium, releasing proteases, free radicals, and pro-inflammatory cytokines [7]. The number of leukocytes, especially neutrophils, in the peripheral blood reflects the severity of the stress and pro-inflammatory response. Leukocytosis in AMI exacerbates myocardial damage and contributes to the development of ALVHF, increases in-hospital and annual mortality [10]. Leukocytosis enhances the processes of pathological post-infarction remodeling of the LV, causes its dysfunction, development of HF [10], and is an independent factor of poor prognosis after AMI [1].

We found the effect of atorvastatin 80 mg on the level of CRP on the 10th day of treatment. There is also evidence of a decrease in this indicator when prescribing simvastatin at a dose of 40–80 mg in patients with non-ST elevation ACS on the electrocardiogram within 14 days to 4 months [1, 2]. Thus, the decrease in the level of CRP and the number of leukocytes in the peripheral blood that we revealed indicates the anti-inflammatory effect of high doses of atorvastatin in the early stages of AMI. The discovered ability of atorvastatin to reduce the incidence of ALVF during the hospital period of AMI and reduce the intensity of inflammatory processes suggested that the drug has a positive effect on myocardial contractility and remodeling of the LV cavity. Therefore, we analyzed the parameters of intracardiac hemodynamics in patients on the 1st day and after 3 months of the disease (Table 2).

Table 2: Indicators of global LV systolic function in patients at baseline (numerator) and after 3 months (denominator)

Index	Group II	Group I
tIVS, %	28,5±0,8 51,5±0,7*	28,7±0,88 48,5±0,4*^
tPWLV, %	32,2±0,7 64±0,7*	31,8±0,8 60±0,6*^
LV EDV, ml	163,3±1,3 164,4±1,6	164,8±1,2 166,5±2,1
LV ESV, ml	87,3±1,4 73,2±1,2*	86,5±1,2 79±1,5
LVMMI, g/m2	110±2,4 118±2,2	110±2,4 121±2,4
LV SV, ml	76±1,3 91±0,9*	78,3±1,5 86,7±1,1
LV EF, %	46,5±0,5 53,4±0,5*	47,3±0,3 51,5±0,4*^
LA, mm	36±1,3 37±1,2	35,5±1,2 37,6±1,1
Vmax LVOT, m/s	0,91±0,03 1,07±0,03	0,82±0,03 0,98±0,03

Note.*-p<0.05 - in comparison with the initial data; ^- p<0.05 - compared with the 1st group.

When studying the indicators of LV remodeling, it was revealed that atorvastatin in high doses positively affects the indicators of LV EDV, LV ESV and LVMMI. According to the dynamics of LV EDV, the patients of the two groups did not differ significantly, although in patients of the 1st group after 3 months there was a slight tendency to dilatation. In patients of the 2-nd group, who took atorvastatin at a dose of 80 mg, a more significant decrease in LV ESV was observed after 3 months (p<0.05). As can be seen from the obtained data, after 3 months, in patients of both groups, an improvement in LV systolic function was recorded in the form of an increase in LV EF. In patients taking high doses of atorvastatin, LV EF increased more significantly. The results of the study indicate that high doses of atorvastatin have a more favorable effect on the indices of postinfarction LV remodeling. During low dose dobutamine stress-echocardiography in group II, 4.2±0.16 asynergic segments restored their contractile function, in group I, 3.88 ± 0.14, since these segments had stunned myocardium (reversible myocardial dysfunction). The remaining asynergic segments did not respond to dobutamine administration, as they showed myocardial necrosis (irreversible dysfunction). Irreversible dysfunction in groups 1 and 2 was detected in 1.6±0.1 and 2.2±0.1 asynergic segments, respectively. The number of dobutamine-responsive segments (segments with reversible dysfunction) in the group of patients treated with atorvastatin at a dose of 80 mg during myocardial reperfusion was significantly higher than in the control group (p<0.05). Dobutamine-non-responsive segments were found more often in patients of the control group (p0.05). The indicator of regional systolic function WMAI at low doses significantly decreased to 1.17±0.03 and 1.25±0.03, respectively (p<0.01). WMAI with the introduction of small doses of dobutamine in patients of the 2nd group decreased more significantly (p<0.05). A significant decrease in WMAI with the introduction of low doses of dobutamine is an important predictor of improvement in left ventricular systolic function against the background of adequate therapy.

Thus, after reperfusion in patients with AMI with ST segment elevation, by echocardiography revealed zones of asynergy, which are not always due to myocardial necrosis. Myocardial asynergy may be due to reversible myocardial dysfunction (stunned myocardium). Carrying out myocardial reperfusion in the infarct-related coronary artery with the simultaneous use of high doses of atorvastatin limits the development of myocardial necrosis, reducing ischemic and reperfusion damage to the myocardium, affects the formation of myocardial stunning, which is a reversible dysfunction, and leads to an improvement in post-infarction remodeling processes of the left ventricle.

CONCLUSIONS

The use of atorvastatin at a dose of 80 mg/day in the first hours after the development of acute myocardial infarction helps to reduce the severity of myocardial reperfusion injury, reduce the number of peripheral blood leukocytes and reduce the severity of an increase in ESR, CRP, thereby reducing severity of reperfusion injury of the myocardium.

Carrying out myocardial reperfusion in the infarct-related coronary artery with the simultaneous use of high doses of atorvastatin helps to limit the development of myocardial necrosis, reducing ischemic and reperfusion damage to the myocardium, and affects the formation of myocardial stunning zones, which are reversible dysfunction. The use of atorvastatin at a dose

of 80 mg/day in the first hours after the development of acute myocardial infarction improves LV systolic function, preventing the progression of postinfarction dilatation of the left ventricular cavity.

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