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THE EFFECTIVENESS OF PRECONDITIONING AND POSTCONDITIONING WITH ADENOSINE IN PREVENTION OF REPERFUSION DAMAGE IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Abstract

The study aimed to evaluate the effectiveness of pharmacological pre-conditioning and post-conditioning with sublingual adenosine in prevention of reperfusion damage in patients with acute myocardial infarction with ST-segment elevation (STEMI). **Material and methods.** In our prospective trial 166 patients with STEMI were randomized to the group of sublingual adenosine administration prior and after percutaneous coronary intervention (n=82) or to the group of standard therapy (n=84). Reperfusion arrhythmia, blood level of troponin T and effectiveness of reperfusion was assessed. **Results.** According to PCI results, angiographic success was achieved in 88.1 % patients of adenosine group and in 92.7 % patients of standard therapy group ($p > 0.05$). The reperfusion arrhythmias rate was significantly low in adenosine group (78 %) compared to the control (92.9 %, $p = 0.013$). The use of adenosine was associated with 25.4 % reduction of life-threatening reperfusion arrhythmias risk ($p < 0.01$). In 24 h after PCI, troponin T level decreased in both groups, more significantly in the group of adenosine administration ($p < 0.05$). The use of adenosine was associated with 8.3 % reduction of myocardial reperfusion damage risk ($p < 0.05$). **Conclusions.** The pharmacological pre-conditioning and post-conditioning with sublingual adenosine in the perioperative period of PCI in patients with STEMI is useful to prevent myocardial reperfusion damage but does not affect the efficiency of reperfusion.

Key words: *acute myocardial infarction, pharmacological pre-conditioning, adenosine, reperfusion damage*

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STEMI — acute myocardial infarction with ST-segment elevation, PCI — percutaneous coronary intervention

Early reperfusion strategy is currently, the cornerstone in the management of patients with acute myocardial infarction with ST-segment elevation (STEMI) [1]. Timely and successful revascularization of the infarct-related artery is the key to limiting the size of cardiac muscle necrosis, slowing down the processes of its remodeling and improving further prognosis [2]. At the same time, the sudden resumption of perfusion in the ischemic area of the myocardium can lead to further damage of the cardiac muscle, decreased contractile function and the onset of life-threatening arrhythmias [3]. In recent years, such adverse effects of intracoronary interventions have been referred to as small myocardial lesions [3, 4]. These lesions generally do not have any specific clinical signs and are

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diagnosed with an increased level of cardiospecific enzymes or the occurrence of severe reperfusion rhythm disturbances.

Effective methods of prevention of myocardial reperfusion injuries have not yet been developed, and clinical studies in this area are isolated. One of the most promising directions in the prevention of the above complications is considered to be the pharmacological protection of the myocardium using adenosine, which is based on the phenomena of pre- and post-conditioning [5]. In some studies, intravenous adenosine administration along with thrombolytic therapy or percutaneous coronary intervention (PCI) led to reduced volume of necrotic myocardium and decreased size of the perfusion defect in patients with acute myocardial infarction [6]. However, intravenous use of adenosine is limited by the complexity of dosing and the need for careful monitoring of hemodynamic parameters, and its efficacy is limited by the rapid degradation of the drug in the bloodstream. Therefore, it is important to search for substances similar to adenosine, but with a more favorable pharmacokinetic profile.

The objective of this study was to evaluate the efficacy of pharmacological pre- and post-conditioning with adenosine-containing drug Advocard in the prevention of reperfusion myocardial damage in patients with STEMI subject to primary PCI.

Materials and methods

A prospective open-label study was conducted involving 166 patients admitted to the Department of Emergency Cardiology, Institute of Emergency and Reconstructive Surgery n.a. V. K. Husak with a diagnosis of STEMI. The inclusion criteria were:

1) age over 18 years;
2) STEMI of the 1st type with duration of less than 12 hours;
3) planned urgent myocardial revascularization by means of PCI;
4) signed informed consent.

STEMI was diagnosed if the patient had an episode of angina in combination with persistent (lasting at least 20 min) ST-segment elevation or new left bundle branch block on the electrocardiogram (ECG) and elevated levels of myocardial injury biomarkers. ST-segment elevation was considered to be significant in terms of ischemia at least in two consecutive leads, if its value at J-point level was ≥ 0.2 mV in men or ≥ 0.15 mV in women in V2–V3 leads and/or ≥ 0.1 mV in other leads.

The exclusion criteria were:

1) use of thrombolytic therapy for myocardial revascularization;
2) conducting PCI procedures before the beginning of the study;
3) myocardial infarction of type 2, 3, 4A, 4B, 5 according to the Third universal definition of myocardial infarction;
4) cardiogenic shock;
5) uncontrolled hypertension (systolic blood pressure ≥ 160 mm Hg);
6) hemodynamically significant bradyarrhythmia (sinus bradycardia with < 55 beats/min > 10 min; atrioventricular block of the 2nd or 3rd degree);
7) permanent atrial fibrillation;
8) implanted pacemaker;
9) history of coronary artery bypass grafting;
10) use of adenosine-containing drugs for the last 30 days;
11) severe asthma;
12) use of sildenafil citrate;
13) severe decompensated comorbidities;
14) pregnancy;
15) alcohol and drug abuse;
16) participation in another clinical trial within the previous 30 days.

The patients were divided into 2 groups by envelope method: the first group included 84 patients in whom PCI was performed with standard therapy without pharmacological protection of the myocardium by triggers of ischemic pre- and post-conditioning; the second group consisted of 82 patients who, for initiation of pharmacological pre- and post-conditioning before performing PCI, were administered sublingually adenosine-containing drug Advocard using the following regimen: 1 tablet, after 30 minutes — 2 tablets, followed by 1 tablet 3 times a day with an interval of 8 hours for 4 weeks. Patients in both groups were administered

a standard drug therapy of STEMI (angiotensin converting enzyme inhibitors, β-blockers, statins, antithrombotic agents, if necessary, nitrates, narcotic analgesics) in accordance with current recommendations.

The efficacy of reperfusion, presence and severity of reperfusion arrhythmias, changes in blood troponin T levels were evaluated in all patients.

Immediate angiographic success was defined as complete (TIMI 3) restoration of blood flow in infarct-related artery in the absence of dissections and thrombosis. The phenomenon of "no-reflow" was defined as the lack of adequate myocardial perfusion after recanalization (TIMI < 3). In addition to TIMI blood flow, a marker of successful reperfusion was also considered to be positive dynamics of the ST-segment on the ECG, which was defined as a decrease in ST-segment height by ≥ 70 % from the baseline in 60 min after intervention. ECG reflection of "no-reflow" phenomenon was considered to be the absence of reduction of ST-segment elevation corresponding to the criteria of successful reperfusion with satisfactory (TIMI 2–3) blood flow through the main infarct-related artery.

The presence and type of reperfusion arrhythmias were assessed using continuous ECG monitoring for 24 hours after PCI using Horizon XVU hemodynamic monitoring device (Mennen Medical, Israel). Analysis of rhythm and conductivity changes was performed according to the classification of Goldberg and Vita, wherein life-threatening disorders included complete atrioventricular block, paroxysmal ventricular tachycardia, fibrillation, flutter and ventricular pause.

Blood troponin T level was determined twice: at baseline, before PCI and in 24 h after intervention by electrochemiluminescence method with immunochemical analyzer Cobas 6000 (e 601 module) using test-system TNT-HS Roche Diagnostics (Germany).

Processing was performed on a personal computer using Microsoft Excel and statistical analysis software packages MedStat and Statistica 6.0. χ^2 and Shapiro-Wilk W tests were used to check the distribution for normality. At normal distribution the quantitative characteristics were presented as mean ± standard deviation (m ± σ), in a case other than normal distribution — as median and 1st, 3rd quartiles (Me (Q1; Q3)). For comparison of two samples of continuous variables subject to the normal distribution law, paired and unpaired Student's t-tests were used while the Wilcoxon test was used for other distribution than normal one. We used the standard method of analysis of contingency tables using the χ^2 criterion to study the distribution of discrete features in different groups and to compare relative values. The reduction of the absolute risk of events was determined with a 95 % confidence interval (CI). Fisher's angular transformation was used for its calculation. In all cases of hypothesis testing, the differences were considered significant at $p < 0.05$.

The study was conducted in accordance with international GCP standards. The study protocol and informed consent form for patients were approved by the local Ethics Committee, Institute of Emergency and Reconstructive Surgery n.a. V. K. Husak (minutes of meeting No. 14 dated 23.09.2013).

Results and discussion

Initially, both groups of patients were comparable in relation to the main clinical and demographic characteristics: gender, age, severity of cardiac pathology and comorbidities (Table 1).

The time from the onset of the episode of angina to hospitalization was on average 4.5 (2; 6) hours in group 1 and 5 (2; 7) hours in group 2 ($p > 0.05$). Time from the moment of hospitalization to revascularization (door-to-balloon) did not exceed 60 minutes in both groups. There were no significant differences in the initial angiographic characteristics of patients between the groups (Table 2).

According to the results of PCI, direct angiographic success was achieved in 88.1 % of patients in group 1 and 92.7 % of patients in group 2 ($p > 0.05$). "No-reflow" phenomenon in PCI outcome was found in 11.9 % of patients in group 1 and 7.3 % in group 2, but the differences in frequency did not reach statistical significance (Table 3).

Table 1. *Patients' initial clinical characteristics*

Characteristic	Group 1 (n=84)	Group 2 (n=82)
Age, years, m±σ	54.0±7.2	52.6±6.9
Males, number of patients (%)	71 (84.5)	68 (82.9)
BMI, kg/m^2, m±σ	29.4±2.8	28.8±2.4
Smoking, number of patients (%)	52 (61.9)	48 (58.5)
Hypertension, number of patients (%)	74 (88.1)	70 (85.4)
Diabetes mellitus, number of patients (%)	16 (19.0)	13 (15.9)
Renal dysfunction, the number of patients (%)	32 (38.1)	40 (48.8)
Dyslipidemia, the number of patients (%)	70 (83.3)	69 (84.1)
Previous cerebral circulation disorders, number of patients (%)	8 (9.5)	6 (7.3)
Previous MI, the number of patients (%)	15 (17.9)	15 (18.3)
Previous PCI, the number of patients (%)	7 (8.3)	8 (9.8)
Preinfarction angina, number of patients (%)	51 (60.7)	43 (52.4)
LV EF, %, Me (Q1; Q3)	42 (40; 46)	43 (40; 46.5)
Time from symptoms onset to admission, h, Me (Q1; Q3)	4.5 (2; 6)	5 (2; 7)
Time from admission to revascularization (door-to-balloon), min, Me (Q1; Q3)	45 (30; 45)	45 (30; 45)
MI localization, number of patients (%):		
Anterior	44 (52.4)	46 (56.1)
Posterior	38 (45.2)	35 (42.7)
Apical	2 (2.4)	1 (1.2)
Killip class, number of patients (%):		
I	62 (73.8)	57 (69.5)
II	18 (21.4)	20 (24.4)
III	4 (4.8)	5 (6.1)

Note: BMI — body mass index, EF — ejection fraction, LV — left ventricular, MI — myocardial infarction, PCI — percutaneous coronary intervention. All differences are not statistically significant (*Ps* > 0.05).

Table 2. *Patients' initial angiographic characteristics*

Characteristic	Group 1 (n=84)	Group 2 (n=82)
Infarct-related artery, number of patients (%):		
Left main coronary artery	1 (1.2)	0
Left anterior descending artery	40 (47.7)	43 (52.4)
Circumflex artery	5 (5.9)	4 (4.8)
Right coronary artery	35 (41.8)	32 (39.0)
Diagonal arteries	1 (1.2)	0
Left marginal artery	2 (2.4)	2 (2.4)
Intermediate artery	0	1 (1.2)
Type of coronary system damage, number of patients (%):		
Single-vessel	35 (41.7)	38 (46.3)
Two-vessel	21 (25)	24 (29.3)
Multivessel	28 (33.3)	20 (24.4)

Note: all differences are not statistically significant (Ps > 0.05).

Table 3. *PCI results*

Characteristic	Group 1 (n=84)	Group 2 (n=82)	Differences between groups
PCI duration, min, Me (Q1; Q3)	60 (50; 70)	60 (50; 75)	p=0.978
Drug-eluting stents, number of patients (%):	12 (14.3)	9 (11)	χ^2=0.17, p=0.684
Nondrug-eluting stents, number of patients (%):	72 (85.7)	73 (89)	χ^2=0.17, p=0.684
Immediate angiographic success, number of patients (%):	74 (88.1)	76 (92.7)	χ^2=0.55, p=0.461
Phenomenon "no-reflow", number of patients (%):	10 (11.9)	6 (7.3)	χ^2=0.55, p=0.461

Note: PCI — percutaneous coronary intervention.

Analysis of changes in ECG also showed no significant differences in the incidence of rapid positive dynamics in ST-segment between the two groups (89.3 % in group 1 vs. 92.7 % in group 2, χ^2=0.24, p=0.623). Thus, the use of adenosine did not have a significant impact on the efficacy of reperfusion in patients with STEMI subject to primary PCI.

One of the myocardial reperfusion injury markers is various arrhythmias that occur in the first hours after the restoration of blood flow in the infarct-related artery. Reperfusion cardiac arrhythmias are often classified as life-threatening, and can be fatal sometimes. In this regard, one of the objectives of our study was to assess the effect of adenosine on reperfusion arrhythmogenesis in the study cohort of patients.

Initially, there were no significant differences in heart rate (HR) between the groups. The median heart rate before PCI in group 1 was 80 [62; 106] min^{-1}, in group 2 it was 78 [68; 110] min^{-1}; after the procedure — 66 [58; 76] min^{-1} and 64 [56; 80] min^{-1}, respectively (p > 0.05). Differences were found in maximum heart rate after PCI: this figure was significantly higher in group 1 (110 [98; 118] min^{-1}) compared to group 2 (101 [90; 106] min^{-1}, p=0.02).

In general, various disorders of rhythm and conduction before PCI were reported in 33 (39.3 %) patients of group 1 and in 28 (34.1 %) in group 2 (χ^2=0.28, p=0.6). During 24 h after PCI their frequency was significantly higher in group 1 (92.9 %) compared to group 2 (78 %) (χ^2=6.21, p=0.013).

In the analysis of the frequency of prognostically unfavorable arrhythmias it was found that in the adenosine group sinus tachycardia with a heart rate > 110 min^{-1} (51.2 % vs. 71.4 %), frequent group and polytopic ventricular extrasystoles (39 % vs. 70.2 %) and idioventricular rhythm (19.5 % vs. 34.5 %, all p < 0.05) developed significantly less frequently.

The prevalence of life-threatening arrhythmias was almost twice lower in group 2 (31.7 %) compared to group 1 (57.1 %) (χ^2=9.86, p=0.002). When analyzing certain types of arrhythmia it was found that patients receiving adenosine rarely experienced paroxysmal ventricular tachycardia (34.1 % of patients, p < 0.05), while in all cases it was monomorphic and unstable. In the comparison group, episodes of ventricular tachycardia were reported in 51 (60.7 %) patients, two of them (2.4 %) experienced torsade de pointes which transformed into ventricular fibrillation. Ventricular fibrillation in the first day after PCI was not reported in the adenosine group, in contrast to the control group, in which it developed in two patients. However, these differences did not reach statistical significance. There were no asystolic episodes in any of groups.

Thus, the use of adenosine was associated with decrease of the frequency of life-threatening reperfusion arrhythmia by 25.4 % (95 % CI 10.3 to 39.0 %, p < 0.05), while in the case of ventricular tachycardia episodes it had the type of monomorphic arrhythmia and was unstable.

We carried out a comparative assessment of the levels of myocardial necrosis biomarker troponin T before and after PCI in two groups. Initially, the concentration of troponin T in the blood did not differ significantly between the groups. One day after PCI its level significantly decreased in both groups, and more significantly — in the 2nd group (Table 4).

Table 4. *Troponin T level before and after PCI, pg/ml, Me (Q1; Q3)*

Characteristic	Group 1 (n=84)	Group 2 (n=82)	Differences between groups
Before PCI	684 (528; 896)	698 (516; 921)	p=0.96
After PCI	264 (128; 356)	168 (105; 286)	p<0.001

Note: PCI — percutaneous coronary intervention.

Four (4.8 %) patients in the 1st group and 1 (1.2 %) patient in the 2nd (χ^2=0.78, p=0.379) reported an increase in troponin T titer by more than 20 % from baseline, which met the criteria for the diagnosis of myocardial infarction of type 4A (PCI-related) in combination with the phenomenon of delayed contrast enhancement of the infarct-related artery and the absence of positive ECG dynamics in these patients. There was no significant decrease in the troponin T level compared to the baseline in 8 (9.5 %) patients in group 1 and 1 (1.2 %) patient in group 2 (χ^2=4.08, p=0.043) 24 h after PCI. However, due to the absence of other clinical, electrocardiographic and angiographic signs of persistent or increasing myocardial ischemia, this finding was regarded as a marker of minor myocardial damage caused by reperfusion.

Thus, the results of the study indicate the presence of infarct-limiting properties in adenosine-containing drug Advocard: its use as an inducer of pre-and post-conditioning is associated with a more pronounced positive dynamics of troponin T levels after PCI and decrease in the risk of reperfusion myocardial damage by 8.3 % (95 % CI 1.2 to 16.5 %, p < 0.05).

The results may be due to increased myocardial resistance to acute anoxia as a result of the beginning of pharmacological pre- and post-conditioning processes initiated by adenosine. It is known that endogenous adenosine production is triggered in conditions of acute ischemia and reperfusion [7]. Currently, four types of adenosine receptors are found on the surface of cardiomyocytes: A1, A2A, A2B and A3. Experimental studies have shown that activation of all four types of receptors is accompanied by the restriction of the necrotic zone and improvement of myocardial function recovery after acute ischemia [8].

The positive effect of adenosine on reperfusion arrhythmogenesis seems to be due to increased electrical stability of the myocardium due to the initiation of endogenous cardioprotection processes. Stimulation of specific adenosine receptors on the surface of cardiomyocytes by the drug leads to the activation of numerous links of the enzymatic cascade focused on implementation of protective mechanisms. The most well-known end points of adenosine-mediated cardioprotection are the opening of ATP-dependent mitochondrial potassium channels and the closure of specific ion channels of the inner mitochondrial membrane. The consequence of these processes is the maintenance of ATP reserves, prevention of cardiomyocyte membrane damage by reactive oxygen intermediates, reduction of intracellular calcium overload, stimulation of nitrogen oxide synthesis and decrease of endothelial dysfunction, which ultimately contributes to the improvement of electrophysiological properties of cardiomyocytes and the prevention of reperfusion arrhythmias [9].

Conclusions

1. The use of adenosine-containing drug Advocard as a trigger of ischemic pre- and post-conditioning in the perioperative period of PCI in patients with STEMI is associated with a significant (p < 0.05) reduction in the risk of myocardial reperfusion damage by 8.3 % (95 % CI 1.2 to 16.5 %) and a decrease in the incidence of life-threatening reperfusion arrhythmias by 25.4 % (95 % CI 10.3 to 39.0 %).

2. The use of pharmacological pre-conditioning with Advocard in the perioperative period of primary PCI does not significantly affect the efficacy of reperfusion and the frequency of the “no-reflow” phenomenon.

Conflict of interests
The authors declare no conflict of interests.

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