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**Research Article**

# Influence of Adenosine-5-Triphosphogluconate-Magnesium Trisodium Salt and Levocarnitine on Clinical Course, Structural and Functional Changes and Myocardial Fibrosis in Patients with Myocardial Infarction

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**Abstract**
Modern strategies of STEMI/NSTEMI management, that include revascularization by coronary stenting, bypass grafting, nowadays are used in 30-40% of urgent patients of such category. The prevalent part of patients is treated by administration of the optimal drug therapy.
**The objective** of the research was to study the influence of adenosine-5-triphosphogluconate-magnesium trisodium salt and levocarnitine on the clinical course of STEMI/NSTEMI.
**Materials and methods**. 100 patients with STEMI/NSTEMI were included into the research. Depending on the therapy scheme, patients were divided into three groups and the control one. Determination of the key parameters was performed initially after hospitalization and at the day of patient discharge.
**Results**. Promising results were shown while slowing the myocardial fibrosing. Limiting of the infarcted and 'stunned' myocardium area resulted in ejection fraction increase, increase of the myocardial reserve, measured by echocardiographic indexes.
**Conclusions**. Decreasing of myocardial fibrosing can be potentiated by the pharmacological postconditioning as well as limiting of the necrotic myocardium area and increase of viable myocardium area. Pharmacological postconditioning is effective and save, that can be proved by the absence of any serious complications.

**Keywords**
myocardial infarction; revascularization; postconditioning; postinfarction remodeling

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## Problem statement and analysis of the latest research

Modern strategies of STEMI/NSTEMI management, that include revascularization by coronary stenting, bypass grafting, nowadays are used in 30-40% of urgent patients of such category. The prevalent part of patients is treated by administration of the optimal drug therapy. The coronary blood flow restoration itself paradoxically leads to myocardial injury and enlargement of the lesion zone up to 50% – so called reperfusion injury phenomenon, that is realized through the endotoxicity of reactive oxygen species, endothelial cells and macrophage activation [1, 2, 3].

One of the possible ways of potentiating of the standard STEMI/NSTEMI treatment scheme can be recently discovered mechanism of preconditioning

and postconditioning. It is proved that these processes are aimed on the adaptation of myocardium to ischemia and protection of myocardium from metabolic damages because of the lasting cycle of ischemia-reperfusion [4]. All known mechanisms of myocardium conditioning converge to the prevention of opening of the mitochondrial permeability transition pore (mPTP), which is crucial and leads to imminent cell death by apoptosis [4]. Extracellular adenosine acts as cytoprotective modulator in physiological and pathological conditions in response to organic or cellular stress, including myocardial ischemia [5]. Nowadays, the influence of adenosine is actively studied in clinical practice (AMISTAD and AMISTAD-II clinical trials), so as levocarnitine, that is endogenously synthetized aminoacid and plays significant role as a cofactor in fatty acids metabolism that results in ATP synthesis [6, 7, 8].

The objective of the research was to study the influence of adenosine-5-triphosphogluconate-magnesium trisodium salt and levocarnitine on the clinical course of STEMI/NSTEMI.

## 1. Materials and Methods

100 patients with STEMI/NSTEMI were included in the research. 25 patients, which formed the control group, received standard therapy. The main group of patients was divided into three subgroups depending on the addition to the standard scheme: 1st subgroup (25 patients) received 30 mg of adenosine-5-triphosphogluconate-magnesium trisodium salt (domestic production drug 'Advocard') 3 times per day orally in addition to the standard therapy; 2nd subgroup (25 patients) received 20 mg of levocarnitine (domestic production drug 'Tivor-L' - levocarnitine mixture with l-arginine) in 1 infusion per day, for 8-12 infusions per course as addition to the standard scheme; 3rd subgroup (25 patients) received both of drugs in the same doses as the addition to the standard scheme. Average age of included patients was 63.6±0.80 years. 64% of patients were men and 36% - women. All patients underwent through standard clinical examinations (clinical monitoring of STEMI/NSTEMI signs – dynamics and changes of the pain syndrome, signs of peripheral hypoperfusion), ECG in 12 standard leads (auxiliary lead systems where used on demand), transthoracic echocardiography with detailed visualization of segmental myocardial contraction (including calculation of special indexes: index of contractile function of myocardium – ICF; index of remaining myocardial reserve – IRMR). ICF was calculated by dividing stroke volume (SV) to end-systolic volume (ESV). IRMR was calculated with the help of I. Sledzevska's (2012) method as the end-systolic volume divided to the end-diastolic volume (ESV/EDV; normally 0.38±0.01 units). In case of ICF lowering to $<$ 25-10% after the treatment, the scheme was considered ineffective. In case of IRMR was $<$ 0.45, sufficient myocardial reserve was observed; 0.45-0.55 meant restrictions of the myocardial reserve; $>$0.56 meant serious restrictions of myocardial reserve. Index of myocardial mass of the left ventricle (IMMLV) was used to characterize the structural changes in myocardium. Also, the laboratory marker of cardiac fibrosis (serum fibronectin) was studied. Statistical analysis included data processing using methods of parametrical and non-parametrical statistics, Student's t-criterium.

## 2. Results and Discussion

Results of the clinical monitoring after treatment course showed (see Table 2), that patients of the 1st subgroup had slightly increased ejection fraction (EF): from 48.43±0.609% to 51.27±0.785% ($p<0.05$), 3rd subgroup showed better dynamics of the EF: from 47.46% to 52.35% ($p<0.05$), while control group did not show credible results: from 48.05% to 48.65% ($p>0.05$). ICF in the 1st subgroup increased from 0.94±0.02 units to 1.06±0.03 units. Even better results were observed in the 3rd group: from 0.90 units to 1.09 units ($p<0.05$). On the contrary, the control group did not show credible results. IRMR showed tendency to decrease in 1st and 3rd subgroups: from 0.51 to 0.48 and from 0.53 to 0.48 units correspondingly ($p<0.05$) that mean more effective involvement of the remaining myocardial reserves. 2nd subgroup and con-

**Table 1.** Dynamics of the main indexes before and after the treatment course.

| Index | Control group | | Main group | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1st subgroup | | 2nd subgroup | | 3rd subgroup | |
| | Before | After | Before | After | Before | After | Before | After |
| LVEF | 48.05 [44.15-50.28] | 48.65 [46.77-50.60]; +1.2% | 48.43 ±0.609 | 51.27 ±0.785; +5.8%* | 51.25 ±1.143 | 53.56 ±1.214; +4.5% | 47.46 [45.27-49.65] | 52.35 [49.53-55.72]; +10.3%* |
| ICF | 0.92 [0.79-1.01] | 0.94 [0.87-1.02]; +2.1% | 0.94 ±0.023 | 1.06 ±0.034; +12.7%* | 0.98 [0.90-1.17] | 1.08 [0.97-1.36]; +10.2% | 0.90 [0.83-0.99] | 1.09 [0.98-1.26]; +21.1%* |
| IRMR | 0.51 [0.49-0.55] | 0.51 [0.49-0.53]; 0% | 0.51 ±0.006 | 0.48 ±0.008; -5.9%* | 0.50 [0.45-0.52] | 0.48 [0.42-0.50]; -4% | 0.53 [0.50-0.55] | 0.48 [0.44-0.50]; -9.5%* |
| IMMLV | 151.21 [137.63-167.79] | 129.84 [118.25-167.47]; -14.2%* | 200.63 ±6.149 | 158.13 ±5.042; -21.2%* | 162.65 ±7.477 | 168.72 ±6.697; +3.7% | 142.93 [129.39-155.41] | 137.78 [128.73-154.31]; -3.7% |
| Fibronectin | 2.24 ±0.131 | 2.43 ±0.124; +8.4% | 1.89 [1.76-2.16] | 1.90 [1.78-2.20]; +0.5% | 1.76 ±0.095 | 1.66 ±0.081; -5.7% | 1.72 [1.47-2.14] | 1.39 [1.12-1.74]; -19.2%* |

*Note:* * - $p<0.05$

trol group did not show credible results. IMMLV credibly decreased in 1st subgroup of the main group and in control group: from 200.63 to 158.13 g/kg/1.73$^2$ and from 151.21 to 129.84 13 g/kg/1.73$^2$ correspondingly ($p<0.05$) what proved the regression of postinfarction hypertrophy and remodeling of left ventricle. Cardiac fibrosis credibly slowed by 19, 2% in 3rd group ($p<0.05$) evaluated by the serum fibronectin level. In the control group this exponent grew up in 24 patients out of 25. The summary of all results indicates on the reducing of the infarction size at the expense of restriction of the 'scar' zone and increase of the viable myocardium area.

## 3. Conclusions

Adenosine-5-triphosphogluconate-magnesium trisodium salt is an effective way to increase the myocardial contractility, correct excessive fibrosis, decrease the size of the myocardial infarction at the expense of limitation of the 'scar' zone, increase of the viable myocardium area. Levocarnitine was not as effective in case of solitary addition to the treatment scheme. Treatment effectiveness essentially increases in case of two drugs addition to the therapy scheme. Cardiac fibrosis in postinfarction period can be slowed down by combined usage of both researched drugs. Application of both drugs did not cause any serious side effect, so it is safe and well tolerated.

## 4. Prospects of Further Researches

A comprehensive research of myocardial postconditioning can be performed to identify to effect of postconditioning in patients that underwent percutaneous coronary intervention (PCI) of coronary artery bypass grafting (CABG) with more severe myocardial reperfusion injury.

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