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Results of the study of efficacy and tolerance of Tivor-L® in combination treatment of patients with non-ST elevation acute coronary syndrome and unstable angina

Mortality in exacerbation of coronary heart disease (CHD), in particular in acute coronary syndrome (ACS), remains relatively high. Administration of conventional medical therapy and the use of methods of recanalization of the infarct-related coronary artery can significantly improve the treatment of this patient population, however, do not always meet the expectations of clinicians. Furthermore, restoration of blood flow in the coronary arteries may be associated with worsening of its damage that emphasizes the problem of protecting the myocardium in patients with ACS. Prevention of the occurrence of ACS complications requires the decrease in the progressive damage of cardiomyocytes and severity of myocardial metabolism disorders arising from the first seconds of ischemia.

With that in mind, the cardiologists are intensively developing the methods for metabolic correction of conditions caused by ischemia/reperfusion in the treatment of acute and chronic forms of coronary heart disease, in particular the methods of myocardial cytoprotection. While earlier research efforts have focused on the study of the metabolic properties of hemodynamically active drugs, recently more and more attention is given to the drugs having antioxidant properties, membrane protectors and catabolic enzyme inhibitors.

They include levocarnitine (L-carnitine) and arginine hydrochloride.

L-carnitine plays an important role in the β-oxidation of fatty acids (FA), that is, in energy production in mitochondria. Thus, L-carnitine acts as a specific co-factor which controls the oxidation rate of long-chain FA and facilitates their transport through the inner membrane of mitochondria. Moreover, L-carnitine takes part in the removal of excess FA from mitochondria, and then from the cytoplasm, thus preventing the development of a cytotoxic effect. In the setting of ischemia, acyl coenzyme A, which balance with free coenzyme A is supported by the action of the so-called carnitine shuttle transporting acyl residues of FA, accumulates in the mitochondria. Removing excess of acetyl groups from mitochondria, L-carnitine promotes formation of malonyl-coenzyme A, which inhibits carnitine shuttle and thereby reduces the rate of β-oxidation of FA in the setting of ischemia.

It has been shown that in CHD, acute myocardial infarction (AMI) and heart failure of various origins, the level of L-carnitine in the myocardium was reduced.

Arginine belongs to a class of conditionally essential amino acids; it is an active and versatile cellular regulator of many vital body functions and has significant protective effects: anti-hypoxic, membrane stabilizing, cytoprotective, antioxidant, and detoxification. Arginine is involved in regulation of intermediary metabolism and energy processes, and plays a role in maintaining hormone balance in the body. Arginine is known to increase blood levels of insulin, glucagon, growth hormone and prolactin; takes part in the synthesis of proline, agmatine, and polyamine; included in the processes of fibrinogenolysis and spermatogenesis. Arginine is a substrate for the formation of N0-synthase — the enzyme that catalyzes the synthesis of nitric oxide in endothelial cells. The drug activates guanylate cyclase and increases cyclic guanosine monophosphate (cGMP) in the vascular endothelium; reduces activation and adhesion of leukocytes and platelets; inhibits the synthesis of adhesion molecules VCAM-1 and MCP-1; inhibits the synthesis of endo-thelin-1 which is a powerful vasoconstrictor and stimulator of proliferation and migration of smooth muscle cells of the vascular wall. Arginine also inhibits the synthesis of asymmetric dimethylarginine — a powerful endogenous stimulator of oxidative stress.

Strong evidence suggests that urgent therapy using intravenous administration of L-carnitine and arginine hydrochloride is a pathogenetically substantiated method that allows reducing the severity of myocardial metabolism disorders in patients with ACS and reperfusion syndrome.

The above determines the relevance and practical significance of this study which evaluated efficacy and tolerance of Tivor-L® (Yuria-Pharm LLC) containing L-carnitine (20 mg) and arginine hydrochloride (42 mg) in combination treatment of patients with non-ST elevation acute coronary syndrome and unstable angina as compared to the group of patients who received background therapy alone.

Study objective and methods

Study design

The study was conducted in accordance with the requirements of the State Enterprise "State Expert Center of the MoH Ukraine" to clinical trials of medicinal products.

This was an open, randomized, comparative, parallel two-group study which included the following phases: screening and treatment (10 days). The study involved 100 patients with non-ST elevation ACS, which were assigned to treatment and control groups in 1:1 ratio.

Patients of treatment group, in addition to background treatment (according to the order No. 164 of the Ministry of Health: sublingual nitroglycerin, aspirin or clopidogrel, analgesics, β-blockers or ACE inhibitors), received Tivor-L® 100 ml intravenously by drip infusion with a rate of 10 drops per minute during the first 10-15 minutes (followed by the increase in infusion rate up to 30 drops per minute) once a day for 10 days. Patients of control group received background therapy alone. In the course of the study, neurometabolics and nootropics were prohibited.

Patients were admitted to the intensive care unit with a diagnosis of non-ST elevation ACS in the first 12 hours from the time of disease onset. **Inclusion criteria:** the presence of typical pain syndrome at rest, lasting more than 10 minutes, or increase in the frequency and severity of angina attacks with the absence or decrease in nitroglycerine effect for the last 24 hours prior to admission in the setting of non-ST-segment elevation. Patients with anterior localization of MI and unstable angina fully met the selected inclusion criteria.

Exclusion criteria:
- hypersensitivity to the components of the study drug;
- pregnancy and lactation;
- degenerative diseases of the central nervous system (Alzheimer's disease, Parkinson's disease, essential tremor);
- renal and hepatic failure;
- diabetes mellitus;
- oncological diseases;
- malignant myasthenia gravis;
- extensive types of allergic dermatitis;
- multiple sclerosis;
- impaired liver and/or kidney function;
- acute thrombophlebitis;
- marked heart beat disorders (tachycardia > 100 beats/min, frequent supraventricular and ventricular premature beats, atrial fibrillation);
- severe respiratory failure;
- pulmonary embolism;
- myocarditis, endocarditis;
- endocrine diseases (Graves' disease, hypothyroidism, adrenal insufficiency);
- participation in another clinical trial of the same substance or of any study drug within 30 days prior to inclusion in this study (any drug that can affect the assessment of the therapeutic effect; administration prior to inclusion in the study of any drug, the use of which is unacceptable for 2 months before the visit);
- likehood of the patients' non-compliance with a protocol or failure to fulfill its requirements, including the provision of informed consent (inability to give informed consent due to mental retardation or language barrier).

According to echocardiography (echoCG) performed at admission, the mean left ventricular ejection fraction (LVEF) did not significantly differ between the groups: in treatment group, the value was 55 ± 10.6%, in control — 54.1 ± 10.5%. The group were not significantly different in terms of intensity of subjective complaints and clinical manifestations of ACS.

Thus, two groups of 50 people who met the criteria and were comparable in the primary selection criteria were included in the clinical study.

Assessment of treatment efficacy

Treatment efficacy was assessed using the following methods:

Laboratory methods: evaluation of markers of myocardial necrosis — troponin T, total creatine phosphokinase (CPK), CPK-MB — every 6 hours during the first day of hospitalization, then the maximum values of the markers were taken into account.

Instrumental methods: 12-lead ECG, echoCG. To study the intracardiac hemodynamics, sectoral echoCG was performed with the calculation of basic parameters of cardiac structure and function in accordance with the recommendations of the American Society of Echocardiography. Mandatory calculation of end-diastolic and end-systolic indices (EDI and ESI, respectively) and LVEF was carried out.

Study end points

Primary outcome
• no clinical signs and ECG parameters of myocardial ischemia;
• stabilization of condition (no myocardial infarction, sudden death).

Secondary outcomes
• evaluation of clinical symptoms of myocardial ischemia over time;
• changes in cardiac enzymes and ECG criteria over time.

Overall efficacy of treatment was assessed by a categorical variable, which description is presented in Table 1.

Assessment of tolerance

Tolerance of the study drug was assessed based on:
• the objective data obtained by investigator in the course of the study. For this purpose, an objective examination of the patients, including the measurement of heart rate (HR), blood pressure (BP), ECG, auscultation of the heart and lungs, and examination of the skin and visible mucous membranes were carried out at each visit;
• the data of laboratory examination performed prior to and upon completion of the treatment with the study drug:
— complete blood count: red blood cells, hemoglobin, hematocrit, white blood cells, platelets, erythrocyte sedimentation rate;
— urinalysis;
— biochemical blood assay (total protein, levels of ALT, AST, cholesterol, creatinine, glucose, cardiac troponins T/I);
• subjective feeling of the patient. At each visit, investigators conducted a patient survey which takes into account the presence and severity of both the projected and unexpected adverse reactions.

The criteria for drug withdrawal were ≥ 3-fold activity of transaminases compared with the upper limit of normal; increased blood creatinine; the occurrence of myalgia, muscle weakness and other symptoms of drug intolerance, and patient refusal to continue treatment.

Methods of statistical analysis of the data obtained

The results of the study were processed using Student's t test, Shapiro-Wilk test, Yates corrected Pearson χ^2, Mann-Whitney test, Fisher test.

Study results

Treatment efficacy
The drug Tivor-L®, prescribed as a part of combination therapy immediately after admission to the hospital, has been found to improve the electrophysiological properties of the myocardium and prevent the occurrence of temporary ECG abnormalities. Within the first hours after onset of AMI, late ventricular potentials (LVP), markers of the so-called arrhythmogenic substrate, were less frequently recorded in patients of treatment group (9.6%) compared to 19.8% of controls. During follow-up, LVP in control group resolved, and in Tivor-L® group — did not occur. This suggests the presence of expressed anti-ischemic effect of the drug, which is confirmed by clinical data.

We observed significant positive changes in the final part of ventricular complex under the influence of therapy with Tivor-L®. In the analysis of standard ECG data and 24-hour ECG monitoring data, heart beat disorders were detected in some patients. There were no significant differences between the groups in the incidence of all forms of arrhythmia syndrome both at baseline, and after treatment, however, in the course of treatment, the incidence of ventricular beat disorders as a group ventricular extrasystole and runs of ventricular tachycardia significantly decreased in treatment group.

During the period of in-patient treatment, all patients showed positive clinical dynamics: reduced frequency and severity of angina attacks, decreased blood pressure, and increased exercise tolerance. As early as on the third day of treatment with the study drug Tivor-L®, anginal pain less frequently relapsed (20.8% of cases in treatment group and 32.0% - in control). At the same time, there was a decrease in demand for the use of narcotic analgesics to relieve recurrent pain syndrome (22.1 and 36.2% cases, respectively). In addition, on the third day after AMI development, the lower incidence of atrioventricular block (4.2 and 12.6%, respectively) was recorded in treatment group as compared to the control.. During the analysis of entire hospitalization period, it was established that patients who received Tivor-L® experienced atrioventricular blocks 3 times less than the controls. The frequency of recording ventricular extrasystole decreased on Day 7 (by 36.2%) and Day 10 (by 44.6%) of the disease.

The main factors determining mortality and unfavorable long-term prognosis in patients with ACS were weight of necrotic myocardium and the rate of formation of necrosis. In order to detect the necrosis in myocardium, cardiac troponins and MB of CPK fraction were determined. The peak of CPK in treatment group was 3.16 ± 0.09 μkat/l, in control group — 3.21 ± 0.12 μkat/l; MB-CPK — 0.24 ± 0.02 and 0.25 ± 0.01 μkat/l, respectively, indicating slight differences in the volume of initially necrotic myocardium. Administration of Tivor-L® within the first hours against conventional therapy of non-ST elevation ACS reduced the time required to reach the peak of CPK activity in patients of treatment group (13.5 ± 0.6 vs. 17.1 ± 0.8 <h in patients of control group); CPK-MB level was 9.9 ± 0.4 and 13.9 ± 0.6 μkat /l, respectively.

Moreover, necrotic lesion area (calculated based on the changes in CPK-MB activity in serum) was 26.4% less in treatment group compared to the control — 45.4 ± 2.1 g/eq. and 61.6 ± 2.9 g/eq. This was due to the reduced period of normalization of CPK and CPK-MB activity in serum by an average of 8.1 and 9.4 hours, respectively. Relatively early onset of the peak of cardiac enzyme activity (CPK, CPK-MB) indicates a more rapid formation of necrosis and the decrease in the time of their leaching — a prevention of further damage of viable cardiomyocytes in patients of treatment group.

Analysis of efficacy by the changes in cardiac biomarkers

Analysis of the changes in markers of myocardial necrosis, such as troponin T, total CPK, CPK-MB, in the study groups using the methods of descriptive statistics is presented in Tables 2 and 3.

As a result, the statistical analysis of the data revealed significant changes in cardiac biomarkers in both groups. Elevated cardiac troponins reflect the damage of cardiomyocytes, which in non-ST elevation ACS may be caused by distal embolization with platelet thrombus formed in the area of rupture or erosion of a plaque.

In patients of treatment group, blood troponin level was 0.15 ± 0.02 ng/ml, in controls — 0.13 ± 0.05 ng/ml. Increased troponin level was accompanied by clinical signs of myocardial ischaemia (chest pain, ECG changes and occurrence of asynergia of the heart wall). In most patients, both in treatment, and control group, troponin levels returned to normal in 48-72 hours and were 0.08 ± 0.02 and 0.1 ± 0.03 ng/ml, respectively.

Table 1. Description of the categories of overall efficacy variable

Category	Description of category
Effective therapy	No clinical signs and ECG parameters of myocardial ischemia. Stabilization of condition (no myocardial infarction, sudden death)
Ineffective therapy	Deterioration of condition and complications

Table 2. Analysis of changes in cardiac biomarkers over time in treatment group using descriptive statistics

Parameter	Time point	Statistical values					
		n	Arithmetic mean	Standard deviation	Median	Min	Max
CPK-MB, μkat/l	Visit 1	50	0.24	0.020	0.22	0.20	0.28
	Visit 5	47	9.92	0.347	9.80	9.08	10.79
CPK, μkat/l	Visit 1	50	3.17	0.100	3.18	2.92	3.39
	Visit 5	47	13.49	0.590	13.38	12.09	15.42
Troponin, ng/ml	Visit 1	50	0.15	0.021	0.16	0.10	0.19
	Visit 5	47	0.08	0.024	0.10	0.03	0.15

Table 3. Analysis of changes in cardiac biomarkers over time in control group using descriptive statistics

Parameter	Time point	Statistical values					
		n	Arithmetic mean	Standard deviation	Median	Min	Max
CPK-MB, μkat/l	Visit 1	50	0.25	0.015	0,25	0.23	0.27
	Visit 5	48	13.87	0.557	13,5	12.53	15.17
CPK, μkat/l	Visit 1	50	3.21	0.108	3,22	2.97	3.44
	Visit 5	48	17.12	0.895	17,02	15.45	19.66
Troponin, ng/ml	Visit 1	50	0.13	0.041	0,15	0.06	0.25
	Visit 5	48	0.10	0.030	0,09	0.03	0.15

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Analysis of efficacy based on the degree of intensity of subjective complaints of patients, which are specific for ACS

The study highlighted a number of positive general clinical shifts, as well as a significant reduction in the intensity of subjective complaints of participants starting from the second visit in both groups of patients. A more rapid regression of pain syndrome was rather observed in treatment group, than in the control. So, in the first 12 hours from the onset of intense pain syndrome, no significant difference in its severity was recorded between the groups. On the 3rd day of treatment as compared with the 1st day, the pain intensity significantly decreased in both groups. From the 7th day of treatment, the degree of pain syndrome started to decline prominently in treatment group as compared to control group. By the end of the follow-up period, this trend maintained. Reduced intensity and decrease in the frequency of angina pain was accompanied by a reduced demand for nitrates in the patients of treatment group. A survey of patients in the course of study showed that the administration of Tivor-L® since the early days of ACS onset had a positive effect on the intensity of subjective complaints of patients. To Day 10, patients of treatment group experienced a significant decrease in the degree of intensity of subjective feelings like anxiety, inner agitation, weakness, pain in the heart or in other parts of the chest, feeling short of breath. The use of Tivor-L® against a conventional therapy of non-ST elevation ACS had a positive effect on basic clinical parameters in combination therapy.

Change in echoCG-parameters in patients with non-ST elevation ACS against different treatments

Prior to admission to the hospital and after 10 days of hospitalization, echoCG was performed in stabilization of condition. The following parameters were determined and assessed: end-systolic and end-diastolic volume and left ventricular dimensions (EDV and ESV; EDD and ESD), EF, left ventricular stroke volume, LV diastolic function. According to echoCG, at baseline both groups were comparable in all studied parameters characterizing both systolic and diastolic LV function. Follow-up did not reveal significant changes in the volume of the LV cavity (EDI evaluated) in both groups. At the same time, patients of treatment group showed a significant increase in LVEF after 7 days of treatment. Assessment of the results of longitudinal echoCG study in treatment group against conventional therapy found that early administration of Tivor-L® had a positive effect on hemodynamics, reducing the dilation of LV cavity, which leads to a decrease in LV ESV on Day 10 of observation. At the same time, control group showed a trend to an increase in EDI on Days 7 and 10 of AMI. LVEF increased in both groups, but the increment on Day 10 of AMI was more significant in treatment group: 9.3 and 6.1%, respectively. Provided echoCG data suggest that the use of Tivor-L® as a part of basic conventional therapy has a reliable and positive effect on LV remodelling in patients with non-ST elevation ACS.

Assessment of overall efficacy of treatment with the study and reference drugs

Overall efficacy of the drugs was assessed using the integrated variable which included the stabilization of the patient, presence of complications, cases of re-infarction, and sudden death. One case of Q-wave MI in patients of treatment group and one case of non-Q-wave MI in controls were recorded. Causes of myocardial infarction were not directly dependent on the treatment and were associated with the duration and intensity of pain syndrome prior to treatment and non-compliance with prescribed limited motor pattern. In both cases, MI proceeded without complications and developed in the first 12 hours after admission. In the total number of observations (95), 2 IM cases accounted for 2.1% with respect to 47 patients of treatment group (2.1%) and to 48 patients of control group (2.0%). None of the groups reported ACS-related deaths.

Based on the results obtained, it can be concluded that the groups significantly differed in the efficacy of treatment.

Therefore, the use of Tivor-L® in treatment group, in addition to significantly earlier stabilization of ACS symptoms, resulted in a significant decrease in early post-infarction angina and life-threatening ventricular tachyarrhythmia (ventricular fibrillation/ventricular tachycardia).

Assessment of exceeding efficacy

The conclusion regarding exceeding efficacy of treatment with the study drug Tivor-L® was made taking into account the confidence intervals (CI). Since the primary efficacy variable was dichotomous, the difference between the proportion of positive results in the groups was calculated; the limits of 95% CI for this difference evaluated; and the lower limit of 95% CI with a limit of the area of exceeding efficacy (0%) compared. The results of calculation are shown in Table 4.

Thus, due to the fact that the lower bound of 95% CI for the difference between the proportion of larger border area exceeding efficiency (0%), it can be concluded that the combination treatment of ACS with the study drug Tivor-L® (Yuria-Pharm LLC) is superior to conventional therapy efficacy.

Analysis of tolerance

Patients tolerated well the intravenous administration of Tivor-L®. Treatment with the study drug as a part of basic therapy had no adverse effect on the quantitative biochemical markers of peripheral blood, characterizing the condition of the liver, carbohy-drate, lipid and nitrogen metabolism. The difference in parameters in patients of treatment and control groups at all stages of the study was not statistically significant. During the study, hemodynamic parameters of patients in treatment and control groups were stable. According to the results obtained, the value of heart rate, systolic and diastolic blood pressure in patients of both groups was not significantly different. In all patients of both treatment and control groups, the drug tolerance was assessed as good. None of the patients reported adverse events, both local and general, the development of which could be related to the study drug Tivor-L®.

Conclusions

1. The use of the study drug Tivor-L®, manufactured by Yuria-Pharm LLC, in addition to basic therapy helps to improve the management of patients with non-ST elevation ACS. In combination treatment with Tivor-L®, a more rapid regression of ACS clinical manifestations is observed

2. The use of the study drug Tivor-L® in treatment of non-ST elevation ACS may stabilize the condition of patients and reduce the incidence of complications.

3. Tivor-L® is well-tolerated by the patients; causes no serious adverse reactions and has no adverse effect on the performance of laboratory tests of blood and urine.

4. Overall efficacy of treatment with Tivor-L® is superior to conventional therapy for patients with non-ST elevation ACS.

The list of references is located in the editorial office.

Table 4. Results of analysis of exceeding efficacy

Statistical index	Value
Probability of type I error, α	0.025
Percentage point of standard normal distribution for α	1.96
Limit of the area of exceeding efficacy, %	0.0
Proportion of positive outcomes for treatment group, %	87.2
Size of treatment group	47
Proportion of positive outcomes for control group, %	66.7
Size of control group	48
Proportion difference, %	20.5
Standard error	8.37
Lower limit, 95% CI	4.1
Upper limit, 95% CI	36.9