

## COMPARATIVE ASSESSMENT OF INTRACORONARY AND INTRAVENOUS INTRODUCTION OF MESENCHYMAL STEM CELLS IN REFRACTORY ANGINA PECTORIS

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*Comparative analysis of the autologous stem cells use by the intravenous and intracoronary injections in patients with refractory stenocardia. Cellular cardiomyoplasty leads to an increase of patients quality of life, improvement of physical load tolerance, daily dose decrease of medicaments, left ventricle ejection fraction increase. Effects of intravenous or intracoronary injections of mesenchymal autologous stem cells are identical.*

**Key words:** *refractory stenocardia, mesenchymal stem cells, intracoronary and intravenous introduction.*

In spite of the wide range of medicamentouse and surgical interventions used in refractory angina pectoris, the treatment results of this pathology leave much to be desired; this fact potentiates the scientists to seek for the new alternative methods of myocardium ischemia treatment. Cellular therapy is a new treatment method for diseases linked with the irreversible death of cellular elements based on the transplantation of different cellular material (embryonic stem cells, autologous and allogenic stem cells of adult organism, fetal progenitory cells) intravenously, in the vessels, nourishing target organ, intraorganic [1,2,3].

**The purpose** is to make a comparative assessment of intracoronary and intravenous introduction of mesenchymal stem cells (MSC) in refractory angina pectoris.

## **Study materials and methods.**

The base of the clinical part of this work consists from the examination results, treatment and dynamic observation results of 45 patients with refractory angina pectoris that were hospitalized in the urgent and recovery cardiosurgery department in the «V.K.Gusak institute of urgent and uecovery surgery NAMS of Ukraine», Donetsk from 2007 till 2013 year. The studies were carried out according to the international bioethical rules presented by the international organizations and associations, and correspond to Helsinki Declaration of the World Medical Association of 2010 year review. We formed three groups; each consisted of 15 patients: in the first group – a control one – the patients got only medicamental therapy; the second group has got a systemic intravenous introduction of autologic mesenchymal stem cells (MSC); intracoronary introduction of autologous MSC was proposed in the third group.

The diagnosis of refractory angina pectoris (RAP) was established on the basis of clinical presentation in patients as well as on the anamnesis, data of invasive and non-invasive examination methods. According to classification NYHA (New York Heart Association), all patients were in II-IV functional class of chronic cardiac insufficiency (CHI). All patients underwent revascularized operations: 27 (60%) had aortocoronary bypass surgery (ACBS); 12 (26,7%) had got stents of coronary arteries and 7 (15,6%) had both ACBS+stents. The disease duration in patients ranged from 7 till 15 years, on an average  $7,42\pm 3,8$ . It should be noticed that all patients got medicamental therapy. The main patients' complaints were: retrosternal pain in 100% of patients'; short breath had 94,7%; quick fatigability in 77,3%; palpitation had 69,3%; from hepatomegaly suffered 49,3% and cough was noticed in 49,3%.

Mesenchymal autologous stem cells of bone marrow the patients received according to the standard methodology in the laboratory of cellular and tissue cultivation of IURS of NAMS of Ukraine [2,3]. MSC in the group with systemic introduction were infused intravenously in dose of 10 million. In the third group (the intracoronary introduction of MSC) all the patients before procedure has selective coronarography with the help of angiographic facilities “Angioscop D” by Siemens (Germany) and “Integris – 3000” (Phillips Holland) under the local anaesthesia (20

ml of Novocaine solution 0,5%) was performed to M. Jadcinski catheter introduction percutaneous puncture of femoral artery according to S. Seldinger; then the catheter was brought closer to the mouth of coronary vessels and a transplant was introduced in the dose of 10 million cells. After the procedure 1,3 and 6 months its efficacy was assessed according to the ultrasound imaging, and the quality of life by Minnesota questionnaire. The statistic processing results of experimental study was made on the computer Pentium V Core Due 2 with the help of the Microsoft Excel 2010, Statistica 6.0 licensed program package. For the monitoring of normality data distribution was used a Shapiro-Wilk test (W); that allowed to use it even with the small sampling ( $n < 30$ ).

### Results and its discussion.

In the study took part the patients with multifocal lesions of coronary vessels and as a rule with myocardium infarction in the anamnesis (Table 1); a part of patients had a formed post-infarction aneurism of left ventricle and heart rhythm disturbances in the form of supraventricular and ventricular extrasystoles; ejection fraction was at an average  $29,8 \pm 5,7\%$ .

**Table 1.** Baseline clinical characteristic in patients with refractory stenocardia

Parameters		1 group		2 group		3 group	
		Abs.	%	Abs.	%	Abs.	%
Myocardial infarction number	1	6	40	8	53,3	5	33,3
	2	4	26,7	4	26,7	7	46,7
Sinus rhythm		13	86,7	15	100	13	86,7
Supraventricular extrasystoles		5	33,3	3	20	4	26,7
Ventricular extrasystoles		3	20	3	20	3	20
LV aneurism		4	26,7	3	20	3	20
Average LV EF, %		28,4 $\pm$ 7,2		31,5 $\pm$ 5,8		31,2 $\pm$ 7,1	
Time from the		2,9 $\pm$ 1,5		3,2 $\pm$ 2,4		2,3 $\pm$ 1,8	

baseline MI, years			
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*Note s.* There were no differences in the clinical characteristics of the studied groups ( $p>0,05$ ).

During the control examinations all studied patients had clinical improvement; it was expressed in the increase of life quality according to the Minnesota questionnaire (MLHFQ), decrease of cardiac insufficiency degree according to NYHA classification and increase of tolerance during the physical exercises on treadmill-test. The maximal effect was observed in one month and was maintained during 3-4 months.

After the ultrasound imaging in the first group during the whole study was a LV EF decrease till  $23,2\pm 5,2\%$  was noticed; in the second group an increase of LV EF during the three months from  $31,5\pm 5,8$  till  $36,7\pm 4,4\%$   $p>0,05$  was observed and remained on the achieved level till the 6 months; then it gradually decreased. In the third group an increase of LV EF from  $31,2\pm 7,1$  till  $37,4\pm 5,2\%$  ( $p>0,05$ ) was also noticed and by the 6 months it began to decrease; in the periods till 6 months LV EF was a little bit smaller than in the second group; and after the 6 months period it decreased till the baseline levels. During this time period the patients reduced the doses of applied medications, it a considerable increase of tolerance to the physical exercises was noticed confirmed by the treadmill-test.

**Conclusions.** As a result of pilot clinical study it was established that the intravenous and intracoronary introduction of MSC increases patients' quality of life, reduces the doses of applied medications, increases left ventricular ejection fraction, and increases tolerance to the physical exercises. Taking into consideration the same clinical effectiveness of intracoronary and intravenous introduction method of MSC as well as the procedure invasiveness during the intracoronary introduction, the expediency of this introduction method application is prejudiced.

## Literature

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## **ПОРІВНЯЛЬНА ОЦІНКА ІНТРАКОРОНАРНОГО ТА ВНУТРІШНЬОВЕННОГО ВВЕДЕННЯ МЕЗЕНХІМАЛЬНИХ СТОВБУРОВИХ КЛІТИН ПРИ РЕФРАКТЕРНІЙ СТЕНОКАРДІЇ**

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*У статті наведена порівняльна оцінка ефективності застосування внутрішньовенного та інтракоронарного введення аутологічних мезенхімальних стовбурних клітин у пацієнтів із рефрактерною стенокардією. Клітинна кардіоміопластика приводить до підвищення якості життя пацієнтів, посилення толерантності до фізичного навантаження, зниження доз лікарських препаратів, а також підвищення фракції викиду лівого шлуночка. Встановлено однаковий лікувальний ефект від внутрішньовенного та інтракоронарного введення трансплантату.*

**Ключові слова:** *рефрактерна стенокардія, мезенхімальні стовбурові клітини, інтракоронарне та внутрішньовенне введення*

# СРАВНИТЕЛЬНАЯ ОЦЕНКА ИНТРАКОРОНАРНОГО И ВНУТРИВЕННОГО ВВЕДЕНИЯ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК ПРИ РЕФРАКТЕРНОЙ СТЕНОКАРДИИ

Эстрин С.И.

*В статье приведена сравнительная оценка эффективности применения внутривенного и интракоронарного введения аутологичных мезенхимальных стволовых клеток у пациентов с рефрактерной стенокардией. Клеточная кардиомиопластика привела к улучшению качества жизни пациентов, усилению толерантности к физической нагрузке, снижению доз лекарственных препаратов, а также к повышению фракции выброса левого желудочка. Установлен одинаковый лечебный эффект от внутривенного и интракоронарного введения трансплантата.*

**Ключевые слова:** *рефрактерная стенокардия, мезенхимальные стволовые клетки, интракоронарное и внутривенное введение.*