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APPROACH OF AUTOLOGOUS INTRAMYOCARDIAL PERIPHERAL BLOOD PROGENITOR CELL TRANSPLANTATION IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY

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ИНТРАМИОКАРДИАЛЬНАЯ ТРАНСПЛАНТАЦИЯ АУТОЛОГИЧНЫХ ПРОГЕНИТОРНЫХ КЛЕТОК ПЕРИФЕРИЧЕСКОЙ КРОВИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ БОЛЬНЫХ С ИШЕМИЧЕСКОЙ КАРДИОМИОПАТИЕЙ

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Перспективной является идея интрамиокардиальной трансплантации аутологичных прогениторных клеток периферической крови пациентам с ишемической кардиомиопатией (ИКМП), которые исчерпали возможности стандартных методов лечения. Пациенты с установленным диагнозом ИКМП были разделены на две группы. В группе 1 (n=29) проводилась интрамиокардиальная трансплантация аутологичных прогениторных клеток периферической крови в комбинации с оптимальной медикаментозной терапией. В группе 2 (n=31) назначалась только оптимальная медикаментозная терапия. Во время контрольных обследований отмечено, что максимальный эффект от трансплантации развивался через 6 мес. после процедуры. Фракция выброса левого желудочка (ЛЖ) увеличилась в среднем на (6±3) %, улучшилась локальная и глобальная сократимость миокарда ЛЖ. Через 18 мес. отмечено увеличение выживаемости в группе, где проводилась трансплантация.

Ключевые слова: прогениторные клетки, ишемическая кардиомиопатия, интрамиокардиальная трансплантация, noga xp.

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Background. Autologous peripheral blood progenitor cells transplantation (PBPCT) in patients with ischemic cardiomyopathy (ICMP) who lack potentialities of standard treatment options seems to have been perspective.

Aims. The main purpose of this study was decreasing of mortality and improving the quality of life of patients with ICMP by developing and application in routine clinical practice the approach of intramyocardial autologous PBPCT in combination with optimal drug therapy.

Materials and methods. Patients with diagnosed ICMP were divided into two groups: autologous transplantation PBPCT in combination with optimal drug therapy (group 1, n=29) versus optimal drug therapy alone (group 2, n=31). Patients of the group 1 received granulocyte colony-stimulating factor (G-CSF) at a dose 5 мg/kg for 5 days. Leukapheresis was performed on the fifth day. Isolation of mononuclear cells (MNC) was provided by Ficoll-Paque 1.077 g/ml density gradient centrifugation. Intramyocardial transplantation was performed by NOGA XP Navigation System and Myostar catheter. Follow up occurred at 1, 3, 6, 12 and 18 months.

Results. During the follow up there was noticed that the maximum effect of intramyocardial transplantation develoed after 6 months after the transplantation. LVEF increased by an average by (6±3)% and improvement of local and global contractility observed. After 18 months-follow-up increasing of survival was noticed.

Key words: progenitor cells, ischemich cardiomyopathy, intramyocardial transplantation, noga xp.

Background

Morbidity and mortality from cardiovascular diseases remains on a high level all around the world. The subsequence of ischemic heart disease that debuts after an acute myocardial infarction or under the influence of chronic ischemia is the development of congestive heart failure. Eventually cellular hypertrophy, extracellular matrix remodeling and dilatation of heart chambers occur that led to ischemic cardiomyopathy (ICMP) development. ICMP is associated with poor quality and shorter life expectancy. To summarize, ICMP is among of the most frequent reasons of the human death [1–3].

Main approaches for treatment of patients with ICMP that exist are: drug treatment or surgical intervention: mechanical revascularization (bypass grafting or percutaneous coronary intervention) and heart transplantation. Surgical methods have shown better outcomes comparably with drug treatment. This fact has been established in big international multicenter randomized trials [4]. Unfortunately, a big group of patients for whom surgical intervention is contraindicated or this approach has not been effective exists. Thus, it is necessarily to develop a new method of treatment of patients with ischemic heart disease that will provide an opportunity to increase life expectancy comparably to standard treatment options [5].

The idea of autologous peripheral blood progenitor cells or autologous bone marrow stem cells transplantation in patients with ICMP who lack potentialities of standard treatment options seems to have been perspective. According to the results of preclinical in vitro studies peripheral blood progenitor and stem cells are able to differentiate into different types of cells and in cardiomyocites in particular. In vivo studies in animal models have shown strong evidence of the efficacy and safety of intramyocardial and intracoronary transplantation of autologous stem cells of different types of myocardial ischemia [6].

Also numerous clinical studies of the application of peripheral blood and bone marrow stem cells have been conducted recently. They have shown the effectiveness of the intramyocardial stem cell transplantation in patients not only with myocardial infarction and ischemic heart disease but also with idiopathic dilated cardiomyopathy [7].

Aims

The main purpose of this study was decreasing of mortality and improving the quality of life for patients with ICMP by developing and application in routine clinical practice the complex approach of intramyocardial autologous PBPCT in combination with optimal drug therapy.

Materials and methods

This was open label controlled randomized clinical trial. Main inclusion criteria were: men and women aged 40–80 with previously diagnosed ICMP with LVEF <35% who were resistant to optimal drug therapy at least for three months before the enrolment and who were not candidate for surgical treatment (or it was not effective). Main exclusion criteria were: coronary artery bypass grafting or percutaneous coronary intervention within 3 months, acute myocardial infarction within 3 months, oncology or hematology diseases within 5 years, pregnancy (table 1). Patients were divided into two groups: intramyocardial transplantation of autologous peripheral blood stem cells in combination with optimal drug therapy (group 1, n=29) versus optimal drug therapy alone (group 2, n=31).

Patients of the group 1 received granulocyte colony-stimulating factor (G-CSF) at a dose 5 мg/kg for 5 days. Leukapheresis was performed on the fifths day (Fresenius COM. TEC, Germany) for collection of primary cytological material (PCM). Isolation of mononuclear cells was provided by Ficoll-Paque 1.077 g/ml (Sigma-Aldrich, UK) density gradient centrifugation. Obtained mononuclear cells were concentrated in 0.9% sodium chloride solution. Final cell concentration must be no less than $200 \cdot 10^6$ MNC per ml. Intramyocardial transplantation was performed using NOGA XP Navigation System and Myostar catheter (Biosense Webster, USA). The dose was divided into 18±3 injections of 0.2 ml per injection. Follow up occurred at 1, 3, 6, 12 and 18 months or by patient's requirement.

Results

During G-CSF — treatment common side effects were flu-like symptoms and joint pains. It was a tendency to worsening angina pectoris symptoms that resulted in increased demand in nitrates. In one case severe chest pain that contributed to additional examination observed.

During leukapheresis common side effects were dizziness, skin and mucous parastesias. In two cases short period of conscienceless was observed. Mean volume of PCM was 153± ±23 ml.

All cell transplants after the processing procedure conformed the requirements of the protocol: they contained minimum $200 \cdot 10^6$ cells per 1 ml, the viability was no lower than 92% and were not contaminated. For the intramyocardial cell transplantation 18±3 points were selected (fig. 1). During the procedure 11 cases of arrhythmias: 3 cases of ventricular fibrillation

Table 1

Some Baseline Characteristics of Patients

Parameters	Group 1, n=29	Group 2, n=31	P
Median age, M±m	67±6	65±5	>0.05
Myocardial infarction, %	51.7	54.8	>0.05
LVEF, M±m	21±5	24±7	>0.05
Functional class, M±m	3.4±0.3	3.5±0.2	>0.05
Diabetes mellitus type II, %	27.6	24.3	>0.05
Hyperlipidemia, %	49.3	47.2	>0.05
Cerebral circulation disorders, %	3.5	2.1	>0.05
Peripheral vessel disease, %	8.2	8.1	>0.05
Chronic kidney disease, %	7.4	7.3	>0.05

and 9 cases of ventricular tachycardia and one case of AV-block were observed during mapping procedure and were not observed during cell implantation. Episodes of ventricular tachycardia were short and resolved without any intervention. In cases of ventricular fibrillation defibrillation was applied successfully. In patient with AV-block pacemaker was implanted immediately.

During the follow up was noticed that the maximum effect of intramyocardial transplantation developed after 6 months after the transplantation. LVEF increased by an average of 6±3% and improvement of local and global contractility observed. After 18 months-follow-up it was noticed the increasing of survival (fig. 2, table 2).

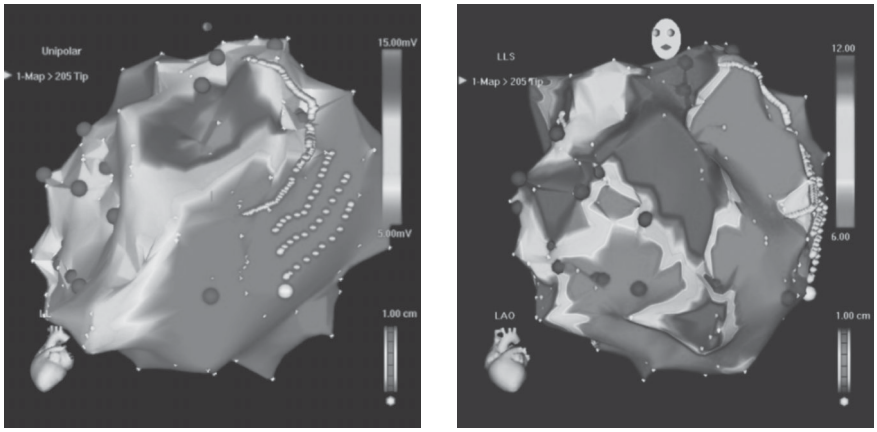
Discussing

Patients suffering from ICMP with low LVEF (<35%) have extremely low life expectancy and quality of life and increasing of LVEF even on 5% (up to 40%) is crucial. Usually people in this cohort have exhausted potentialities of drug as well as surgical methods of treatment. Although these patients are somatically unfit, intramyocardial transplantation of autologous progenitor cells is to be not only safe but also effective and cheap procedure for them.

Although during G-CSF treatment worsening of angina pectoris symptoms and increased demand in nitrates was observed, these complications were not life threatening. Apparently those effects were related to increased viscosity of blood due to bone marrow stimulation. They were not associated with ST elevation or cardiac enzymes elevations. In one case with severe chest pain additional examination revealed L_4-L_5 pathology, thus pain was related to common side effects of G-CSF administration.

Leukapheresis is routinely used in order to collect cells for autologous or allogenic hematopoietic stem cell transplantation in patients with hematological diseases. In our study the procedure of leukapheresis had some differences. Because of low LVEF loss of blood for extracorporal volume could be hemodinamicaly significant. Preventive saline infusion could not be used because of severe heart failure. On the other hand citrate used for the anticoagulation could lead to hypocalcaemia and as a result to arrhythmias. Sometimes allergic reactions could occur.

We provided leukapheresis after premedication with dexamethasone and diphenilhidramin in order to prevent side effects. During the procedure frequent side effects were: dizziness, weakness, parastesias and were related to mechanisms



a *b*

Fig. 1. Left ventricle NOGA XP Navigation System mapping: *a* — a unipolar voltage map; *b* — ventricular contractility map. The spots mark the site of implantation of progenitor cells

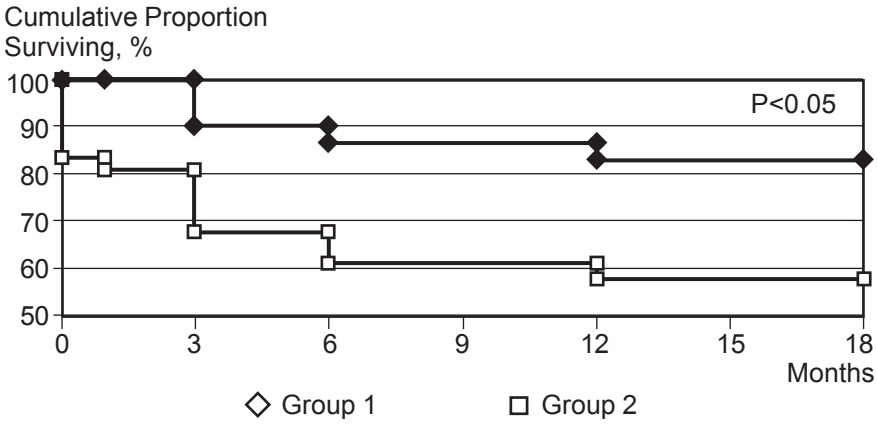


Fig. 2. Kaplan-Meier curves survival in both groups

Table 2

Dynamics of some characteristics of LV's function

Parameters	LVEF, %		EDV, ml	
	Gr 1	Gr 2	Gr 1	Gr 2
Baseline	21±5	24±7	249±15	230±14
1 month	22±6	25±9	243±11	233±10
3 months	27±4*	27±7	239±14	239±13
6 months	29±5*	25±5	212±12*	237±12
12 months	28±6*	23.±4	210±16*	240±15
18 months	27±4*	22±8	224±14	243±17

Note. * — P<0.05.

described above. Generally these complications resolved without any intervention. Only in one case allergic reaction on citrate observed. After GCS infusion all symptoms resolved but we were obliged to discontinue the procedure. Thus, leukapheresis is safe procedure for somatically unfit patients is preferable than bone marrow aspiration for obtaining progenitor cells but patients should be under continuous medical staff supervision during the procedure.

Protocols of treatment of ICMP usually contain diuretics thus patient are usually dehydrated. Therefore hematocrit of primary cytological material was high. As a result hypercoagulation of PCM observed. To prevent hypercoagulation we additionally added citrate to PCM in ratio 1:10 relatively before the processing. Main advantage of the isolation of mononuclear cells by density-gradient centrifugation is low cost; therefore this method could be used to reduce expenses. Eventually all patients sustained the procedure successfully and followed to the NOGA XP mapping procedure.

Electromechanical mapping and intramyocardial progenitor cells transplantation with NOGA XP Navigation System is highly precise method. Although during NOGA XP mapping procedure 11 cases of arrhythmias were observed they were not life threatening and were observed only during mapping procedure. During cells implantation none of side effects were observed.

Conclusion

1. Method of the isolation of autologous peripheral blood progenitor cells in patients with ICMP is safe procedure and give an opportunity to obtain enough amount of progenitor cells for the intramyocardial implantation.

2. Intramyocardial autologous peripheral blood progenitor cells transplantation with NOGA XP Navigation System is highly precise and reliable method.

3. Autologous peripheral blood progenitor cells improve local and global contractility of the left ventricle, increase survival of patients with ICMP.

4. Approach of autologous intramyocardial peripheral blood progenitor cell transplantation advisable to perform to the patients with ischemic cardiomyopathy that are resistant to standard treatment options.

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