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ORIGINAL ARTICLE

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Long-term results of isolated transmyocardial laser revascularization in combination with the intramyocardial autologous bone marrow stem cells injection

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Abstract
To evaluate the long-term results of TMLR using a CO^2 laser in combination with intramyocardial injection of ABMSC as an isolated procedure in patients with the end-stage coronary artery disease, the study included 20 patients (90% male), with a mean age of 58.4 ± 8.7 years. To assess the long-term results, patients were examined in a hospital. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Seattle Angina Questionnaire (SAQ) were used. The evolution of laboratory and instrumental indices, as well as medical therapy, was assessed. The end points of the study were death, acute myocardial infarction (AMI), repeated myocardial revascularization, recurrent hospitalizations due to coronary artery disease, and stroke. The changes in angina functional class were also evaluated. The median of follow-up period was 54 (36; 83) months, that is, 4.5 years. The analysis of the evolution of echocardiographic data showed the absence of statistically significant changes in the following parameters: left ventricular end-diastolic diameter (EDD) ($p = 0.967$), end-systolic diameter (ESD) ($p = 0.204$), end-diastolic volume (EDV) ($p = 0.852$), end-systolic volume (ESV) ($p = 0.125$), and left ventricular ejection fraction (LVEF) ($p = 0.120$). The patients continued to regularly take the main groups of medications. Nitrate consumption was significantly reduced ($p < 0.001$). Significant positive dynamics were observed in the changes in angina functional class. At the baseline, all patients had angina III FC, in the long term, 3 patients had II FC, 11 patients had I FC, and 6 patients had no angina. Clinical outcomes (mortality, recurrent myocardial infarction, stroke) were absent during the follow-up period. There were two cases of repeated myocardial revascularization. Regression analysis revealed that SYNTAX score was associated with the clinical outcome "repeated revascularization." TMLR in combination with intramyocardial injection of ABMSC is a safe method to achieve a statistically significant antianginal effect and reduce the need for "nitrates," which in turn improves the quality of life and reduces the frequency of hospitalizations due to coronary artery disease. These results can be achieved with strict adherence to the certain indications for the intervention.

Keywords Coronary artery disease · Transmyocardial laser myocardial revascularization · Autologous bone marrow stem cells, · Chronic heart failure · CO2 laser

Introduction

IHD is the leading cause of death and disability of the working-age population in many countries all over the world. The standard of treatment for coronary artery disease is the medical treatment, as well as methods of endovascular (stenting of the coronary arteries) and surgical (aorto-coronary bypass) myocardial revascularization. Despite this, there is a category of patients to whom drug therapy does not bring relief, and to carry out stenting of the coronary arteries or coronary artery bypass grafting is not technically possible, due to the nature of the lesion (calcification, diffuse atherosclerosis, previously performed CABG, with the inability to re-bypass).

Currently, alternative methods for the treatment of coronary artery disease are being actively introduced around the world for whom it is not possible to perform direct myocardial revascularization [1–3]. Alternative methods of myocardial

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revascularization include surgery transmyocardial laser revascularization (TMLR) in combination with intramyocardial introduction of autologous bone marrow stem cells (ABMSC). The essence of the proposed method is the formation of transmural channels in the myocardium (in the pool of the coronary artery which could not be revascularized) with CO^2 or holmium laser, with intramiocardial injection of autologous bone marrow stem cells.

Thus, according to meta-analyses and randomized clinical trials [1–6], TMLR, when compared with optimal medical therapy, is associated with a significant improvement in the clinical status of patients: improved angina functional class, reduced repeated hospitalizations, and major adverse cardiac events.

Novel and actively studied method for the treatment of coronary artery disease, both in end-stage chronic heart failure (CHF) and in acute myocardial infarction (AMI), is the administration of stem cells. Embryonic stem cells and autologous bone marrow stem cells are the most widely used. More than 10 years ago, the scientific world began the first studies of bone marrow stem cells in patients with cardiovascular pathology [7], in the hope that stem cell transplantation will open new ways in the management of CHF. Stem cell delivery into the myocardium was carried out in different ways: intramyocardial injection, through the coronary sinus or coronary arteries, as well as intravenously. Since then, a large number of stem cell therapy studies have been reported with varying results [8], most of which have led to only minor improvements [9].

Relying on the synergism of TMLR and intramyocardial injection of ABMSC, both methods were combined in the form of an isolated procedure [10–12] or in addition to CABG in end-stage CAD [13]. These studies resulted in a new treatment method, which is considered by many experts, as an option in this category of patients.

In Russia, the largest experience in the use of TMLR and stem cells has been accumulated in the Bakulev Scientific Center for Cardiovascular Surgery. A prospective, randomized clinical trial (RENAISSANCE) is currently underway to study the contribution of each of the individual methods, TMLR and ABMSC, in addition to CABG in patients with incomplete myocardial revascularization [14].

However, TMLR and stem cell therapy remain highly debatable. Research in this area is still in progress, trying to answer questions about the mechanisms of the effectiveness of TMLR and stem cell injection. Moreover, there are no practical guidelines on the use of this method.

Some experts refer to this method with certain "skepticism," citing the results of the studies [15], casting doubt on the effectiveness and safety of the TMLR procedure. The presence of unresolved issues, publication of new studies, as well as a small number of patients in the studied groups confirms the relevance of the topic and also serves as the basis for further and more precise study of this problem.

The aim of this study was to evaluate the long-term results of TMLR using a CO^2 laser in combination with intramyocardial injection of ABMSC as an isolated procedure in patients with the end-stage coronary artery disease.

Material and methods

The study included 20 patients (18 men), mean age 55.4 ± 8.6 years, who underwent the TMLR surgery in combination with intramyocardial introduction of ABMSC in the Bakulev Scientific Center of Cardiovascular Surgery, at the period from 2010 to 2015. All patients had a diffuse nature of coronary artery disease, involving the distal bed, with the lack of technical possibility of direct myocardial revascularization and no effect of optimal antianginal therapy. The presence of at least one coronary artery pool with preserved blood flow, as well as a satisfactory myocardial contractility (left ventricular ejection fraction (LV EF) > 40%), was important during selection of patients for this procedure.

Contraindications for the operation were bone marrow disease, acute myocardial infarction or acute coronary syndrome, LV EF < 40%, life-threatening arrhythmias, and concomitant pathology in the stage of decompensation.

Initial clinical, laboratory, and instrumental parameters of patients are presented in Table 1. It should be noted that six patients underwent attempts of endovascular myocardial revascularization unsuccessfully, which was the indication for this procedure. The average SYNTAX score was 45.7 ± 12.4, which characterizes the severity of coronary lesions.

In the long-term period, all 20 patients (100%) were examined. The average age at that point was 58.4 ± 8.7 years. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Seattle Angina Questionnaire (SAQ), evaluating the most important aspects of the quality of life of patients with CAD, were assessed before intervention and during follow-up. ECG, echocardiography, and medical therapy were assessed. The end points of the study were death, acute myocardial infarction (AMI), repeated myocardial revascularization, recurrent hospitalizations due to coronary artery disease, and stroke. The changes in angina functional class were also evaluated.

The stage of preparation of stem cells

Trepanobiopsy of the ilium was performed in the preoperative period according to the standard scheme, with a bone marrow intake of 35–40 ml. Later, the following procedures were performed sequentially in laboratory conditions: layering the bone marrow to the fikoll solution, collecting "clouds" of mononuclear stem cells after centrifugation, washing them in a solution of water-salt buffer (PBS, pH 4,2), lysing erythrocyte impurities (if necessary!), and counting the number of

Table1 Clin ical and instrumental characteristics of the patients and intraoperative parameters

Parameters	Value (n = 20)
Age, years	55.4 ± 8.6
Sex:	
- Male, n	18
- Female, n	2
Body mass index, kg/m2	30.1 ± 2.9
CCS, class	3 (3; 3)
CHF according to NYHA, class	3 (3; 3)
Prior myocardial infarction, n (%)	12 (60)
Hypertension, n (%)	18 (90)
Peripheral atherosclerosis, n (%)	12 (60)
Diabetes mellitus, n (%)	2 (10)
Smoking, n (%)	14 (70)
COPD, n (%)	1 (5)
Dyslipidemia, n (%)	8 (40)
Attempt of endovascular revascularization	6 (30)
EDD, cm	5.34 ± 0.54
ESD, cm	3.4 (3.2; 3.6)
EDV, ml	125 (117.5; 158.5)
ESV, ml	46.5 (41.5; 55)
LVEF, %	64.5 (60.0; 67.5)
SYNTAX Score, units	45.7 ± 12.4
MLHFQ, units	24 (12; 34)
SAQ PL, units	64.5 (40.0; 74.4)
SAQ AS, units	62.5 (50.0; 80.0)
SAQ AF, units	60 (50; 75)
SAQ TS, units	61.9 (54.4; 88.8)
SAQ DP, units	33.3 (33; 58)
Intraoperative parameters	
Duration, hours	1.90 ± 0.69
Amount of perforations, units	24 ± 5
Frequency of perforations in the walls:	
- lateral, n (%)	19 (95)
- anterior, n (%)	17 (85)
- apex, n (%)	12 (60)
- posterior, n (%)	9 (45)
ABMSC volume, ml	3 (3; 4)
ABMSC amount, mln	91.5 (67; 115)

Note. Data are presented as M ± SD for normally distributed data or Me (Q1; Q3) for non-normally distributed data

isolated cells which is the final preparation of the finished solution for injection in autologous serum of the patient.

The operational phase

The operation was performed under general endotracheal anesthesia with the access from left-sided anterior-lateral thoracotomy. The incision was performed in the fifth intercostal space. Pericardiotomy was carried out after visualization of the pericardium. The required number of perforations in the myocardium was performed using a CO^2 laser after revision of the left ventricular areas and comparison with radionuclide computed tomography data (Fig. 1a).

We used high-power CO^2 laser "Cardiolaser" (state scientific and practical enterprise "Istok–laser", Fryazino, Moscow oblast, Russia). The depth of laser penetration was previously measured on the organic glass material (plexiglass), so that the perforations were through, but did not exceed a certain length, in order to avoid injury of the underlying anatomical structures. The power of laser exposure was 1000 W, wavelength is 10,600 nm, and its speed ranged from 20 to 5 ms, which allowed to perform a through hole with the diameter of 1 mm within one heart cycle.

The sign of the transmural perforation was a stream of blood from the cavity of the left ventricle, which was also controlled by transesophageal Echo-CG (when the laser beam penetrates into the cavity of the LV interaction with blood occurs, which is displayed on the monitor as appropriate additional echo signals). The short pressure with a cloth was enough for hemostasis, and if necessary, we used hemostatic suture (with Prolene 5/0 thread).

Further, a concentrate of autologous bone marrow stem cells with a volume of 200 μl per injection (Fig. 1b) was injected around the area of laser perforations.

The operation ended with the drainage of the pleural cavity and suturing of the pericardium and wound layer by layer.

The postoperative period

The main aspect of postoperative management of these patients was the prevention of infectious and thromboembolic complications. Prevention of infectious complications was carried out perioperatively and ended after 6–7 days of the patients transfer from the intensive care unit (at the time of discharge). It included antibacterial and antifungal therapy and daily dressings of the postoperative wound. Drugs used for prevention are broad-spectrum antibiotics (protected penicillins – amoxiclav, cephalosporins class 3 – ceftriaxone) and antifungal drugs (fluconazole). Anticoagulant therapy was carried out throughout the time of inpatient treatment under the control of APTT, with the addition of antiplatelet therapy.

Statistical analysis

Normality tests were performed to determine whether data were normally distributed. Further analysis was carried out using parametric and nonparametric tests, depending on the data distribution. Data are presented as M ± SD for normally distributed data or Me (Q1; Q3) for non-normally distributed data. For comparison of two dependent samples, the nonparametric Wilcoxon test and the parametric two-tailed Student's

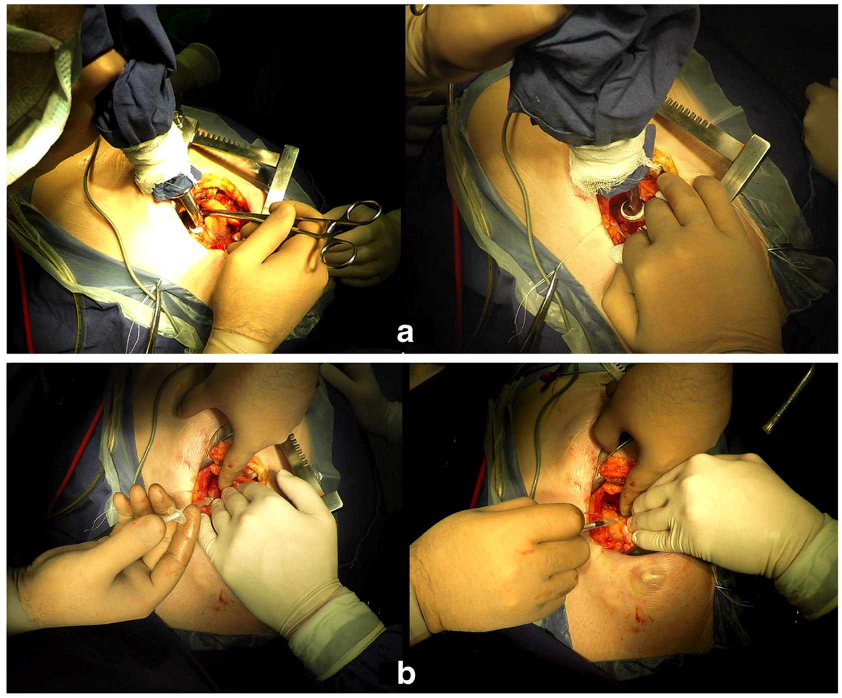

Fig. 1 Stages of TMLR procedure combined with intramyocardial injection of ABMSC: (a) exposure and laser treatment of the left ventricular posterior wall; (b) ABMSC injection in the area of transmyocardial laser revascularization in the left ventricular anterior wall [16]

t-test were used. Multiple variable dependencies were studied using multivariate regression analysis. A 95% confidence interval was utilized. Software packages Microsoft Office Excel 2007 and STATISTICA 10.0 (Statsoft, USA) were used.

Results

The median of follow-up period was 54 (36; 83) months, that is, 4.5 years. The analysis of the evolution of echocardiographic data showed the absence of statistically significant changes in the following parameters: left ventricular end-diastolic diameter (EDD) ($p = 0.967$), end-systolic diameter (ESD) ($p = 0.204$), end-diastolic volume (EDV) ($p = 0.852$), and end-systolic volume (ESV) ($p = 0.125$) (Table 2).

Data from the MLHFQ did not reveal statistically significant changes in these patients ($p = 0.952$). However, according to the results of the SAQ, there were significant changes in the scores of anginal stability (SAQ AS) ($p < 0.001$), anginal frequency (SAQ AF) ($p < 0.001$), treatment satisfaction (SAQ TS) ($p = 0.009$), and disease perception (SAQ DP) ($p < 0.001$). The score of physical limitation was without significant dynamics (SAQ PL) ($p = 0.181$) (Table 2).

Medical therapy remained virtually unchanged. The patients continued to regularly take the main groups of medications. Nitrate consumption was significantly reduced ($p < 0.001$): only three patients in the long-term continued to use nitrates (Table 2).

Significant positive dynamics were observed in the changes in angina functional class (Fig. 2). At the baseline, all patients had angina III FC; in the long term, 3 patients had II FC, 11 patients had I FC, and 6 patients had no angina.

Table 2 The results of laboratory and instrumental indices in patients after TMLR in combination with ABMSC injection

Parameter	Baseline	Long-term	p
Echocardiography			
EDD, cm	5.34 ± 0.54	5.4 ± 0.53	0.967
ESD, cm	3.4 (3,.2; 3.6)	3.6 (3.2; 3.8)	0.204
EDV, ml	125 (117.5; 158.5)	130 (116.5; 155)	0.852
ESC, ml	46.5 (41.5; 55)	51 (41; 66)	0.125
LVEF, %	64.5 (60; 67.5)	62 (58; 65)	0.120
The quality of life			
MLHFQ	24 (12; 34)	22 (12; 30)	0.952
SAQ PL, units	64.5 (40; 74.4)	70 (60; 80)	0.181
SAQ AS, units	62.5 (50; 80)	100 (100; 100)	< 0.001
SAQ AF, units	60 (50; 75)	90 (82; 100)	< 0.001
SAQ TS, units	61.9 (54,4; 88,8)	72 (62.5; 84)	0.009
SAQ DP, units	33.3 (33; 58)	62.5 (50; 80)	< 0.001
Medical therapy			
Antiplatelets, n (%)	20 (100)	20 (100)	0.987
Beta-blockers, n (%)	20 (100)	20 (100)	0.987
ACEI, ARB, n (%)	12 (60)	11 (55)	0.507
Diuretics, n (%)	13 (65)	13 (65)	0.969
CCB, n (%)	4 (20)	3 (15)	0.199
Statins, n (%)	19 (95)	20 (100)	0.214
Nitrates, n (%)	20 (100)	3 (15)	< 0.001

Note. Data are presented as M ± SD for normally distributed data or Me (Q1; Q3) for non-normally distributed data

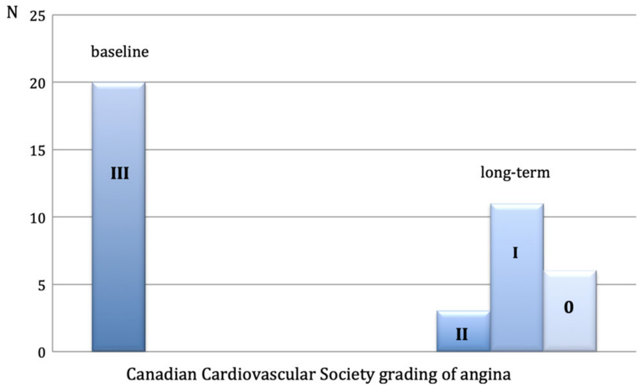

Fig. 2 Distribution of angina functional class (CCS classification) at the baseline and in the long-term period in patients after TMLR in combination with ABMSC injection

Table 4 The results of regression analysis for the clinical outcome "repeated revascularization"

Parameter	Regression coefficient β	Standard error	t	p
SYNTAX score	0.665	0.181	3.663	0.005
Sex	−0.506	0.248	−2.036	0.072
Procedure time	−0.291	0.189	−1.530	0.161
Number of perforations	−0.219	0.250	−0.682	0.519
Age	−0.171	0.253	−0.622	0.549
LVEF before procedure	−0.157	0.238	−0.557	0.591
Weight	−0.064	0.251	−0.255	0.804
Number of ABMSC	0.046	0.214	0.26	0.834

Note: Adjusted R^2 = 0,47, p < 0,05

In addition, clinical outcomes, such as mortality, recurrent MI, repeated myocardial revascularization, and stroke, were evaluated (Table 3).

Regression analysis revealed that only SYNTAX score among all clinical and instrumental indices was associated with the clinical outcome "repeated revascularization" (Table 4).

Discussion

During the entire follow-up period (4.5 years), the mortality rate was 0%; AMI and stroke were not observed. In two cases, it was necessary to perform repeated myocardial revascularization. It is important to note that revascularization was performed because of the progression of initially hemodynamically insignificant coronary artery atherosclerotic lesions that led to the development of symptoms in these patients.

An interesting fact was that in a multivariate regression analysis, only SYNTAX score among all clinical and instrumental indices was associated with the clinical outcome "repeated revascularization." This connection in our opinion is quite understandable. The SYNTAX score calculator was designed to assess anatomically complex lesions of the coronary arteries (CA) in patients with stenosis of the left main CA and three vessel disease. Accordingly, the SYNTAX score is directly proportional to the extent of atherosclerotic lesions, its significance, degree of calcification, and involvement of the distal vessels. Thus, the risk of CAD progression is higher in patients initially belonging to the group with the highest SYNTAX score. The high-risk group includes patients with the SYNTAX score > 32 points. In our study, 2 patients who underwent repeated myocardial revascularization had the SYNTAX score of 72 and 63, respectively.

Table 3 The frequency of major adverse cardiovascular events in the long-term period in patients after TMLR in combination with ABMSC injection

Cardiovascular event	Frequency
Mortality, %	0
Prior MI, %	0
Repeated myocardial revascularization, %	10
Stroke, %	0

The results obtained by analyzing data from the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Seattle Angina Questionnaire (SAQ) deserve attention. Comparing the results of instrumental indices and data from questionnaires, it can be assumed that in the long-term, the clinical effect was clearly achieved – improvement in the angina functional class and decrease in nitrates use. It resulted in the improvement in the quality of life, which is confirmed by the analysis of the SAQ: the scores of anginal stability (SAQ AS), anginal frequency (SAQ AF), treatment satisfaction (SAQ TS), and disease perception (SAQ DP) improved significantly.

There were no statistically significant changes in LVEF (p = 0.120). It can be explained by the fact that the baseline LVEF in all patients was within the normal range – the median was 64.5%. The evolution of other echocardiographic parameters was also without statistical changes: left ventricular end-diastolic diameter (EDD) (p = 0.967), end-systolic diameter (ESD) (p = 0.204), end-diastolic volume (EDV) (p = 0.852), and end-systolic volume (ESV) (p = 0.125).

Some early studies have demonstrated high intrahospital and 30-day mortality (up to 20%) when performing TMLR [17]. Horvath KA and Mannting F et al. defined several factors that were associated with an increased mortality risk. The main risk factor was heart failure: in several studies, the mean LVEF was less than 30%. The authors also identified unstable angina, mitral regurgitation, and the absence of at least one coronary artery with preserved blood flow as risk factors [18–22].

Based on the above data, when determining indications for TMLR in combination with ABMSC injection, we consider satisfactory LVEF as one of the important criteria. We explain this by the fact that the procedure is associated with a myocardial injury and that patients must have some "functional reserve" suggesting a negative effect of the procedure on the contractility of the myocardium in the postoperative period [16, 23].

After many years of research, there is still no full explanation for the mechanisms of TMLR efficacy in the early and late postoperative periods. There are several assumptions, including neoangiogenesis, myocardial denervation, the theory of "reference points," and the placebo effect. Theories of neoangiogenesis, denervation, and the placebo effect are repeatedly described in the literature [24–27].

Cardelli M. hypothesized that the long-term mechanism of the procedure efficacy is that there is a redistribution of strain during systole in the myocardium of the left ventricle. Fibrous transmyocardial bands, formed after some time at the sites of laser channels, serve as fixation points. The author compares them with "columns in the Gothic cathedral." Because of these bands, the strain in the LV myocardium is redistributed, compensatory hyperkinesia in areas adjacent to hypokinetic decreases, and the myocardium contracts more evenly, which leads to lower oxygen and nutrient consumption and, consequently, a decrease in the intensity of angina [28].

Conclusion

The achieved results are probably the result of a combination of described mechanisms, some of which are important in the early postoperative period and others in the long-term period.

Analyzing the results of studies on the use of TMLR and ABMSC, as well as the data obtained by us, there is reason to believe that TMLR procedure in combination with ABMSC administration is an effective method for the treatment of certain patients with CAD. Strict selection of patients for this intervention, considering indications and contraindications, is essential in achieving positive results. TMLR in combination with ABMSC injection is a safe method that allows to achieve a statistically significant antianginal effect and reduces the need for "nitrates," which in turn improves the quality of life and reduces the frequency of hospitalizations due to coronary artery disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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