Original article

Immediate effects of isolated transmyocardial laser revascularization procedures combined with intramyocardial injection of autologous bone marrow stem cells in patients with terminal stage of coronary artery disease

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Abstract: *Aim* — to reveal the immediate results of the transmyocardial laser revascularization (TMLR) using CO_2-laser along with the intramyocardial injections of autologous bone marrow stem cells (ABMSC) in patients with end-stage coronary lesions who cannot be completely revascularized with either percutaneous catheter intervention (PCI) or coronary artery bypass graft surgery (CABG).
Materials and Methods — There were 20 patients with coronary artery disease (CAD) (mean age 55.4±8.6 years; data presented as mean with standard deviation – M±SD) enrolled in this prospective observational study. 90% were men. All were in angina NYHA class III. Arterial hypertension was presented in 90%, peripheral atherosclerosis in 60%. Other 60% of the patients were post-myocardial infarction, 70% were current smokers and the mean SYNTAX Score was 45.7±12.4. All patients had normal left ventricular ejection fraction and volumes calculated echocardiographycally. Around the zone of CO_2-laser impact were injected ABMSC concentrate 200 µl per injection.
Results — All surgeries done off-pump via left-sided anterolateral thoracotomy approach and CO_2-laser with the mean duration of 114±41 minutes. Magnetic resonance imaging data was compared to the left ventricle (LV) wall segments to perform the laser holes. A sign of transmural perforation was the blood jet from the holes in the LV wall. We executed 24±5 perforations and injected 91.5 (67, 115) mln of ABMSC (data presented as median with interquartile range) per patient. Perforations performed on the lateral, anterior and posterior LV walls in 95%, 85% and 45% respectively and on the apex in 60%. The number of the holes did not prolong the time of the surgery (r=–0.09; Spearman correlation). Three (15%) patients had non-fatal complications in the early postoperative period. There was no correlation between these complications and the baseline clinical characteristics or intraoperative parameters. Mortality was 0%. Length of the intensive care unit stay was 1 day and total hospital stay was 6.7±0.7 days (M±SD).
Conclusions — TMLR with intramyocardial autologous stem cells injections in patients with end-stage CAD is safe. This procedure can be done in the most severe group of patients who cannot be completely revascularized with either PCI or CABG surgery. Futher investigation is needed to assess the effectiveness of the procedure.

Keywords: coronary artery disease, transmyocardial laser revascularization, CO_2-laser, autologous stem cells bone marrow.

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Introduction

Patients with coronary artery disease (CAD), who show hemodynamically significant coronary artery lesions according to coronary angiography, can be conventionally divided into three groups. Patients, who can have a complete myocardial revascularization, represent the first group. The second group includes patients with incomplete myocardial revascularization, in which it is impossible to perform myocardial revascularization in one or several beds due to diffuse lesion of distal flow, calcinosis or small diameter of coronary arteries (less than 1 mm). According to different data, the frequency of such cases amounts to 15-25% [1]. According to the literature data, the frequency of re-hospitalizations, coronary artery re-interventions and mortality rate is higher in case of incomplete myocardial revascularization with reference to the complete myocardial revascularization procedures [2-4]. The most severely ill patients with CAD, for whom none of the methods of direct myocardial revascularization can be applied, represent the third group. According to different data, the incidence of this patient group equals approximately 3% from the total amount of patients with CAD [1]. The optimal drug therapy in these cases is either inefficient, or has an unstable effect [2].

Table 1. Clinical and instrumental characteristics of the patients

Parameters	*Value (n=20)*
Age, years, M±SD	55.4±8.6
Sex, %:	
- Male, n (%)	18 (90)
- Female, n (%)	2 (10)
Body mass index, kg/m^2, M±SD	30.1±2.9
CCS, class, Me (Q_1, Q_3)	3 (3, 3)
CHF according to NYHA, class, Me (Q_1, Q_3)	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, M±SD	5.34±0.54
ESD, cm, Me (Q_1, Q_3)	3.4 (3.2, 3.6)
EDV, ml, Me (Q_1, Q_3)	125.0 (117.5, 158.5)
ESV, ml, Me (Q_1, Q_3)	46.5 (41.5, 55.0)
LVEF, %, Me (Q_1, Q_3)	64.5 (60.0, 67.5)
SYNTAX Score, units, M±SD	45.7±12.4
MLHF-Q, units, Me (Q_1, Q_3)	24 (12, 34)
SAQ PL, units, Me (Q_1, Q_3)	64.5 (40.0, 74.4)
SAQ AS, units, Me (Q_1, Q_3)	62.5 (50.0, 80.0)
SAQ AF, units, Me (Q_1, Q_3)	60 (50, 75)
SAQ TS, units, Me (Q_1, Q_3)	61.9 (54.4, 88.8)
SAQ DP, units, Me (Q_1, Q_3)	33.3 (33.0, 58.0)

M±SD is mean with standard deviation. Me (Q_1, Q_3) is median with interquartile range.
CCS, Canadian Cardiovascular Society Classification for Exertional Angina; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; EDD, end-diastolic diameter of left ventricle; ESD, end-systolic diameter of left ventricle; EDV, end-diastolic volume of left ventricle; ESV, end-systolic volume of left ventricle; LVEF, left ventricular ejection fraction; MLHF-Q, Minnesota Living with Heart Failure Questionnaire; SAQ, Seattle Angina Questionnaire; SAQ PL, physical limitation scale; SAQ AS, angina stability scale; SAQ AF, angina frequency scale; SAQ TS, treatment satisfaction scale; SAQ DP, disease perception scale.

One of the alternative methods of surgical treatment of this patient cohort is transmyocardial laser revascularization (TMLR) with intramyocardial injection of autologous bone marrow stem cells (ABMSC). This procedure is performed using different types of lasers and with various fractions of stem cells. It can be performed both as an isolated procedure, and in addition to coronary artery bypass graft surgery (CABG) in the coronary artery bed not acceptable for revascularization.

The most common types of lasers for TMLR are a CO_2 and a holmium laser (Ho: YAG). The Food and Drug Administration (FDA) has approved application of these two devices for TMLR in the USA: a CO_2-laser unit (PLC Medical Systems, Inc, Milford, MA) and a holmium laser (SolarGen TMR Ho:YAG Laser System, CardioGenesis Corporation, Foothill Ranch, CA, USA) [5]. In Russia, high-power domestically produced CO_2 lasers called Perfokor (Institute on Laser and Information Technologies of the Russian Academy of Sciences, Russia) and Cardiolaser (State Research and Development Enterprise Istok-Laser, Fryazino, Moscow Region, Russia) are widely used.

The source of stem cells for this procedure is autologous bone marrow due to its easy accessibility. Moreover, unlike the use of placental and embryonic stem cells, this does not cause any ethical issues.

The world literature data regarding the isolated TMLR procedure combined with intramyocardial injection of ABMSC for diffuse damage of coronary arteries are rather scarce. The existing publications are significantly limited to a small amount of observations.

So far, there are no international clinical guidelines for performing TMLR with ABMSC, both as an isolated procedure and in combination with CABG.

Certainly, the issue considered is quite essential for clinical practice and may trigger further scientific research.

The domestic (Russian) experience of using TMLR is most well described in literature by the Bakoulev Scientific Center for Cardiovascular Surgery (Moscow, Russia) [6-12]. The institution has gained the experience of applying a CO_2 laser in various combinations for surgical treatment of CAD: both as an isolated procedure and in addition to CABG in case of incomplete myocardial revascularization (over 1160), in combination of TMLR with ABMSC injection both independently (20 patients) and in addition to CABG (72 patients) [13].

The objective of this study was to evaluate the immediate effect of TMLR in combination with intramyocardial injection of ABMSC as an isolated procedure in patients with terminal stage of CAD.

Material and Methods

Patients

As a part of the pilot study (2010-2015), 20 TMLR surgeries in combination with intramyocardial injection of ABMSC were performed at the Department of Surgical Treatment of Interactive Pathology of Bakoulev Scientific Center for Cardiovascular Surgery (Moscow, Russia) as isolated procedures for patients with CAD and diffuse lesions of coronary arteries involving the distal flow.

The inclusion criteria were as follows: presence of coronary artery lesions, which cannot be revascularized either by the endovascular method, or by means of CABG; exertional angina of functional class III-IV with a background of the best medical therapy. An important part is the presence of at least one coronary artery bed with the preserved blood flow, as well as satisfactory myocardial contractility (left ventricular ejection fraction (LVEF) >40%).

The exclusion criteria comprised the following factors: bone marrow diseases, acute myocardial infarction or acute coronary syndrome, heart failure (LVEF <40%), life-threatening arrhythmias (paroxysmal ventricular tachycardias, hemodynamically significant supra-ventricular tachycardias), decompensated diabetes mellitus, decompensated co-morbidities.

Besides, all patients underwent myocardial radionuclide tomography (scintigraphy) to evaluate regional myocardial perfusion, ischemia area in the target zone and cicatrical changes. Additionally, the following scales were used to evaluate the most important aspects of life quality of the patients with CAD: the SYNTAX Score scale for evaluating severity of coronary bed disease, the EuroScore II scale for evaluating cardiovascular operative risk, MLHF-Q (stands for Minnesota Living with Heart Failure Questionnaire) and SAQ (Seattle Angina Questionnaire).

The baseline clinical, laboratory and instrumental data of the patients are provided in *Table* 1.

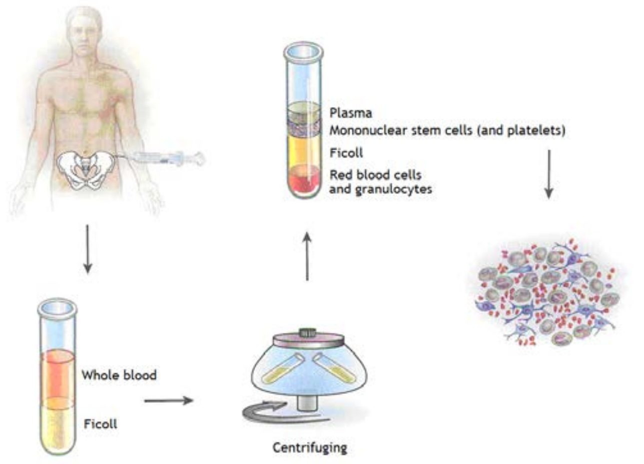

Figure 1. The outline of ABMSC preparation in the pre-operative period.

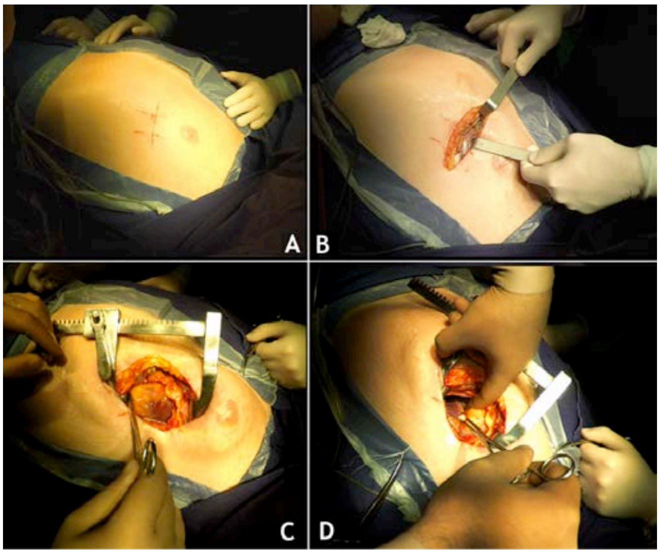

Figure 2. Stages of isolated TMLR procedure combined with intramyocardial injection of ABMSC (part 1): A) the surgical field with marking for a surgical approach; B) the pleural cavity exposed after incision of soft tissues using intercostal approach; C) exposure of the left ventricular apex and anterior wall after pericaridotomy; D) exposure of the left ventricular posterior wall after pericaridotomy.

The study included patients aged 55.4±8.6 years (data presented as mean with standard deviation – M±SD); 90% of them were men. All of them had a high class of exertional angina and chronic heart failure. Hypertension was observed in 18 patients (90%), previous myocardial infarction in 12 patients (60%), peripheral atherosclerosis in 12 patients (60%), and 14 patients (70%) were smokers. Six patients had an unsuccessful attempt of endovascular myocardial revascularization; as a result, they were included in this study. The mean SYNTAX Score was 45.7±12.4 (M±SD), which emphasized a high severity of coronary bed disease in the patients.

According to the quality of life questionnaire, a significant reduction of exercise tolerance, both due to chronic heart failure and exertional angina, as well as moderate stability (SAQ AS – Angina stability scale) and angina frequency (SAQ AF – Angina frequency scale) were observed in the patients of the studied group. Besides, the disease perception score (SAQ DP) reduced dramatically.

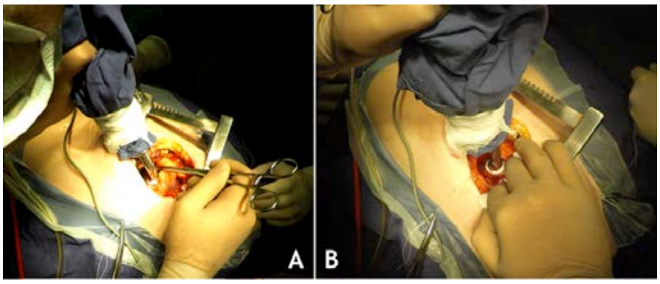

Figure 3. Stages of isolated TMLR procedure combined with intramyocardial injection of ABMSC (part 2): A) exposure and laser treatment of the left ventricular posterior wall; B) exposure and laser treatment of the left ventricular anterior wall.

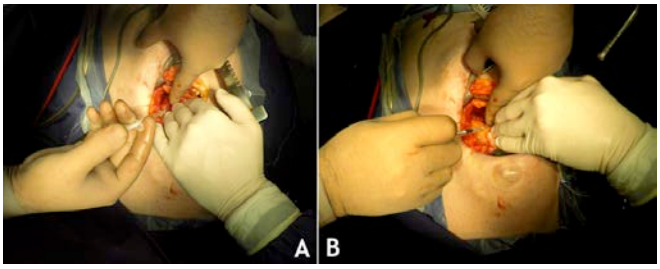

Figure 4. Stages of isolated TMLR procedure combined with intramyocardial injection of ABMSC (part 3): A) ABMSC injection in the area of transmyocardial laser revascularization in the left ventricular posterior wall; B) ABMSC injection in the area of transmyocardial laser revascularization in the left ventricular anterior wall.

The echocardiography data reported a preserved LVEF, normal dimensions and volumes of cardiac cavities.

Stem cells preparation

At the pre-operative stage, a punch biopsy of the ilium was performed with harvesting of 35-40 ml of bone marrow. Further, a number of procedures was done in a laboratory settings (bone marrow aspirate layering over Ficoll solution, collection of mononuclear stem cell "cloud" after centrifuging, flushing of the cells in a water-saline buffer (PBS, pH 4.2), lysis of red blood cell contamination (if necessary), calculation of isolated cells) and final preparation of the solution ready for administration in autologous serum of the patient (*Figure* 1).

Operative stage

The surgery was done under general endotracheal anesthesia with the approach through the left anterolateral thoracotomy. The incision was performed in the fifth intercostal space (*Figure* 2A). After visualization of the pericardium, pericardiotomy was performed. For better exposure, retractors were applied along the incision edges (*Figure* 2B). After inspecting the left ventricle parts and comparing it to the radionuclide computed tomography data (*Figure* 2: D and C), the required amount of myocardial perforations was done using a CO_2-laser (*Figure* 3).

Laser penetration depth was preliminarily measured using organic glass (Plexiglas), to ensure that the perforations were penetrating but did not exceed the particular length to avoid injuring anatomical substructures. The laser power was 1000 W, and its velocity ranged from 20 to 50 ms, which allowed making a penetrating perforation with the diameter of 1 mm within one cardiac cycle. The transmural perforation was evidenced by a blood spurt from the left ventricular cavity, which was also monitored by transesophageal echocardiography (when a laser beam penetrates the ventricular cavity, it interacts with blood, which is displayed on the device monitor in the form of corresponding additional echo-signals). It is sufficient to provide brief pressure with a wipe for hemostasis; if necessary, hemostatic suture is applied.

Further, ABMSC concentrate was injected around the area of laser perforations, 200 µl per injection (*Figure* 4).

The surgery was finished with draining the pleural cavity and suturing the pericardium and the wound layer-by-layer.

Postoperative period

The key aspect of postoperative patient management is prevention of infectious and thromboembolic complications. Prevention of infectious complications was done during the perioperative period and finished 6-7 days after transferring the patient from the intensive care unit (by the moment of discharge). The drugs used for prevention included broad-spectrum antibiotics (inhibitor-protected penicillins – amoxiclav, class 3 cephalosporins – ceftriaxone), antifungal medications (fluconazole). Anticoagulant therapy was performed during the entire period of in-patient treatment with the activated partial thromboplastin time (APTT) control, complemented with antiplatelet therapy.

Statistical analysis

First, the normality of the obtained data distribution was determined. The strictest criterion, Shapiro-Wilk W test, was used. The further studies of relationships were conducted by means of parametric and non-parametric statistics depending on the type of distribution (normal or non-normal distribution). The data are presented as mean with standard deviation, M±SD, for normal value distribution or as median with interquartile range, Me (Q_1, Q_3, for non-normal value distribution. Bonferonni adjustment was used to compare more than two groups. Correlation relationships were evaluated on the basis of Spearman's rank correlation coefficients. Reliability of statistical evaluation was set to no less than 95%. The Microsoft Office Excel 2007 and STATISTICA 10.0 (Statsoft, USA) software packages were used.

Results

The surgery duration in our group averaged 1.90±0.69 hours. In most cases, perforations were made in the lateral and anterior walls, less frequently – in the apex and the posterior wall of the left ventricle (*Table* 2). Increase in surgery duration was not associated with the amount of perforations (r = -0.09, p>0.05; Spearman's correlation).

In the early postoperative period, non-lethal complications were observed in 15% of cases; among them there were two cases of respiratory failure and one case of heart failure. Respiratory failure was considered a complication if the patient had to be left with the prolonged artificial ventilation for more than 48 hours. Number of significant correlation with the initially existing pathology of respiratory system was detected.

Besides, no significant correlation between the development of any complications listed above and the initial clinical or intraoperative parameters was detected.

A tendency to size and volume reduction of cardiac cavities was reported after the surgery. In the early postoperative period, this dynamics was still non-significant (*Figure* 5: parts 1-4). LVEF in the early postoperative period reduced in a statistically significant way (p=0.002; *Figure* 5: part 5).

Table 2. Intraoperative parameters

Parameters	*Value (n=20)*
Duration, hours, M±SD	1.90±0.69
Amount of perforations, units, M±SD	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, Me (Q_1, Q_3)	3 (3, 4)
ABMSC amount, mln, Me (Q_1, Q_3)	91.5 (67, 115)

M±SD is mean with standard deviation. Me (Q_1, Q_3) is median with interquartile range.

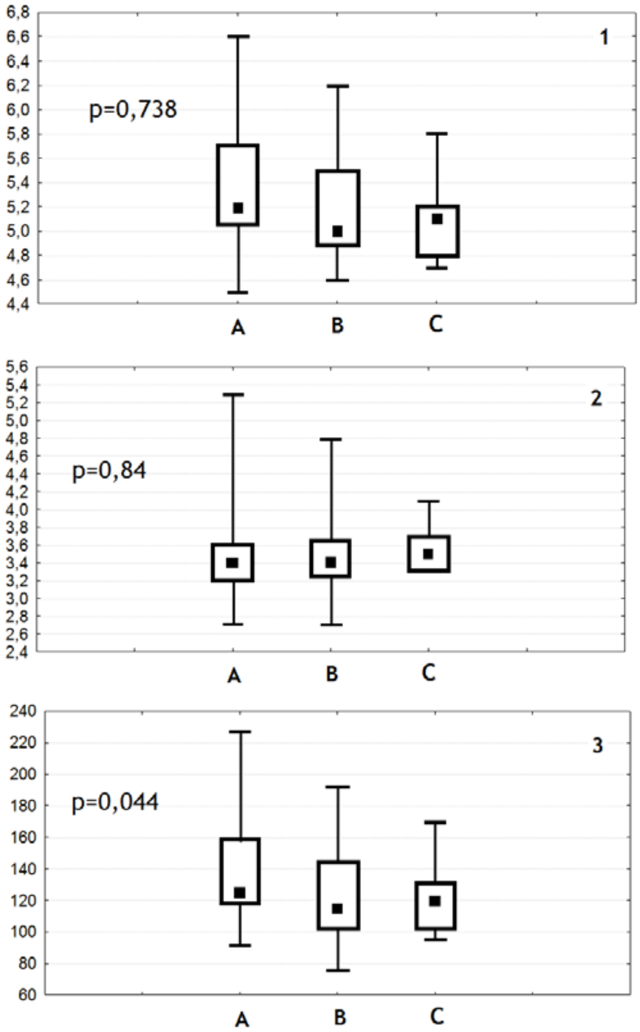

Figure 5. Dynamics of echocardiography parameters. 1 – End-diastolic diameter (A – before surgery, B – on the first day after surgery, C – on the day of discharge from the department). 2 – End-systolic diameter (A – before surgery, B – on the first day after surgery, C – on the day of discharge from the department). 3 – End-diastolic volume (A – before surgery, B – on the first day after surgery, C – on the day of discharge from the department).

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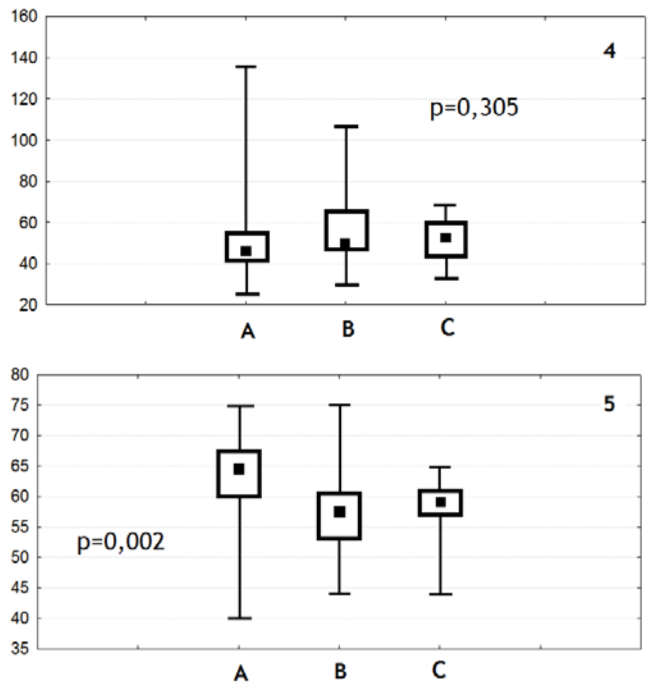

Figure 5. Dynamics of echocardiography parameters (*continuation*). 4 – End-systolic volume (A – before surgery, B – on the first day after surgery, C – on the day of discharge from the department). 5 – Left ventricular ejection fraction (A – before surgery, B – on the first day after surgery, C – on the day of discharge from the department).

Discussion

According to the literature data, application of a CO_2 laser for TMLR in combination with various ABMSC subpopulations shows good immediate and long-term results: functional activity in this category of IHD patients increased [14, 15].

In our study, we analyzed 20 patients with the terminal stage of CAD who underwent TMLR with intramyocardial injection of ABMSC. We obtained good results: a low complication rate (15%) and no lethal cases.

Changes of cardiac chamber volumetric parameters at the early postoperative stage had a tendency to decrease without statistical significance, which is most likely due to the short observation period. Probably, in the longer term, the dynamics of heart volumetric parameters may become statistically significant.

LVEF reduction in the early postoperative period results from a surgical intervention with a traumatic impact on the myocardium. It is important to consider it when selecting patients for this procedure, since some previous studies showed rather high hospital and 30-day mortality (up to 20%) when performing TMLR. Some researchers distinguish several factors that are associated with the increased risk of mortality. Among them, the main risk was heart failure (in several studies, the average LVEF was no greater than 30%). It was followed by unstable angina, significant mitral regurgitation and absence of at least one coronary artery bed with the preserved blood flow [16 - 21]. Thus, the presence of the above conditions should be a criterion for excluding patients from undergoing TMLR. The patients should have a certain “functional reserve” to overcome a negative impact of the surgery itself on myocardial contractility in the early postoperative period.

The volume and amount of injected ABMSC in the patients from our group is similar to the results of other studies. In average, we used approximately 90 mln cells in 3-4 milliliters of autologous serum.

Reyes et al. showed the similar results. They used TMLR with ABMSC in 14 patients with refractory angina [22]. As a result, intramyocardial injection of ABMSC in the area of laser perforation was accompanied with satisfactory immediate (no hospital mortality cases) and medium-term results (from 2 to 12 months) – there were no mortality cases, and decrease in angina functional class was reported (from 3.2±0.5 to 1.4±0.5, p=0.004). However, it should be noted that the authors used a holmium laser unit.

Conclusion

TMLR using a CO_2 laser combined with intramyocardial injection of ABMSC is a modern trend in cardiac surgery for patients with the terminal stage of CAD. Numerous studies of performing TMLR with the injection of stem cells (intracoronarily, intramyocardially) [23, 24] as isolated procedures revealed their abilities of inducing angiogenesis and improving clinical outcomes in patients with the terminal stage of CAD.

The results obtained in the course of this study allow stating that this surgery is safe in case of a thorough patient selection; it is technically simple to perform and can be repeated.

To confirm the synergism of TMLR with the ABMSC injection it is necessary to evaluate the long-term results in this patient group, as well as to conduct large randomized clinical studies.

Supplementary files

Video 1. Isolated TMLR procedure combined with intramyocardial injection of ABMSC.

URL: https://youtu.be/RR6z4rL9Z8w

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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