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Influence of intracoronary injections of bone-marrow-derived mononuclear cells on large myocardial infarction outcome: quantum of initial necrosis is the key

Uticaj intrakoronarne primene mononuklearnih ćelija poreklom iz koštane srži na ishod velikog infarkta miokarda: veličina inicijalne nekroze je ključ

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Abstract

Background/Aim. Autologous bone-marrow-derived intracoronary injection of mononuclear cells (MNC) modestly improved left ventricular ejection fraction (LVEF) in the selected patients after acute ST elevation myocardial infarction (STEMI). Major determinants of stem cell therapy outcome in the subacute phase of STEMI still remain unknown. Therefore, the aim of this study was to determine modifying factors for the outcome of stem cell therapy after STEMI. **Methods.** Eighteen patients in the stem cell therapy group and 24 patients in the control group with the successfully reperfused first large STEMI (LVEF ≤ 40%) were enrolled in the study. The stem cell group was submitted to autologous bone-marrow-derived MNC injection between 7–12 days after MI. Left ventricular ejection fraction and infarction size at baseline and after 4 months were determined by echocardiography and scintigraphy examination. Age, pain onset to reperfusion time, admission glycemia, maximum lactate dehydrogenase (LDH) activity and C-reactive protein level, baseline LVEF and infarction size, and the number of MNC injected were compared between patients with and without significant improvement of LVEF and decrease of myocardial infarct size after 4 months. **Results.** In the stem cell group, patients with the improvement of LVEF for more than 5.1% had significantly lower levels of LDH than patients without such improvement (1689 ± 139 *vs* 2133 ± 215 IU/L, $p < 0.001$) and lower baseline infarction size on scintigraphy (26.7 ± 5.2 *vs* 34.9 ± 3.7%, $p < 0.001$). Such dependence was not found in the control group. **Conclusion.** In the patients with first large STEMI intracoronary injection of autologous bone-marrow-derived MNC leads to the significant decrease of myocardial infarction size but not the significant improvement of LVEF after four months. Higher serum LDH levels after STEMI and very large baseline infarction size are predictors of failure of stem cell therapy in our group of STEMI patients.

Key words:
myocardial infarction; stem cell transplantation; regeneration; treatment outcome; ventricular disfunction, left; l-lactate dehydrogenase.

Apstrakt

Uvod. Primena autologne intrakoronarne implantacije matičnih ćelija poreklom iz koštane srži kod izabranih bolesnika sa infarktom miokarda (IM) sa ST elevacijom dovela je do skromnog poboljšanja ejekcione frakcije leve komore (EFLK). Nepoznato je koji faktori utiču na rezultat ćelijske terapije u akutnom IM. Cilj rada bio je da se utvrde faktori koji utiču na ishod lečenja *stem* ćelijama posle IM. **Metode.** Osamnaest bolesnika činilo je ekperimentalnu, a 24 kontrolnu grupu sa prvim velikim infarktom miokarda (EFLK ≤ 40%) i uspešnom reperfuzijom. Eksperimentalna grupa primila je intrakoronarne injekcije suspenzije mononuklearnih ćelija (MNĆ) od 7. do 12. dana nakon IM. I EFLK i veličina infarkta mereni su između 5. i 7. dana i u 5. mesecu od IM. Životno doba bolesnika, vreme od početka bolova do reperfuzije, glikemiju na prijemu, maksimalnu aktivnost laktat-dehidrogenaze (LDH) i nivo C-rektivnog proteina, broj datih MNĆ, kao i bazalni nivo EFLK i veličinu infarkta poredili smo između grupe bolesnika sa značajnim povećanjem EFLK (>5,1%) i bez njega. **Rezultati.** Bolesnici sa ćelijskom terapijom kod kojih je registrovano značajno poboljšanje EFLK imali su značajno niže maksimalne aktivnosti LDH (1689 ± 139 *vs* 2133 ± 215 IU/L, $p < 0,001$) i manju početnu infarktnu zonu na scintigrafiji miokarda (26,7 ± 5,2 *vs* 34,9 ± 3,7%, $p < 0,001$) od onih kod kojih nije registrovano

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značajno poboljšanje EFLK. Ovakva zavisnost nije registrovana u kontrolnoj grupi bolesnika. **Zaključak.** Bolesnici sa prvim velikim IM sa ST-elevacijom kod kojih se registruje značajno poboljšanje EFLK nakon primene matičnih ćelija sa poreklom iz koštane srži u subakutnoj fazi IM imaju manju aktivnost LDH i niži defekt perfuzije na scintigrafiji miokarda od bolesnika kod kojih primena ove terapije nije dovela do željenog rezultata.

Ključne reči:
infarkt miokarda; transplantacija matičnih ćelija; regeneracija; lečenje, ishod; disfunkcija leve komore; laktat dehidrogenaza.

Introduction

Several randomized clinical studies evaluating intracoronary application of autologous bone-marrow-derived stem cells in the subacute phase of ST elevation myocardial infarction (STEMI) have showed modest improvement of global left ventricular ejection fraction (LVEF), and moderate improvement of regional myocardial function and perfusion [1–7]. Several factors may hypothetically determine the success of bone-marrow-derived stem cell therapy after myocardial infarction (MI). Age of patients, timing from pain onset to reperfusion, timing of stem cell therapy, the number and quality (viability and subpopulation) of injected cells, initial size of infarction, inflammatory response to necrosis and the route of cell delivery are only some of the potential modifying factors which can influence the results of stem cell therapy after STEMI. Elderly patients have lower bone marrow stem cell capacity [8]. Longer duration of critical ischemia, especially at the large myocardial area without developed collaterals resulted with greater necrosis, inflammation, thinning and remodelling of infarcted left ventricle wall. Too early application of cells may bring them in the very hostile environment, during the time of extreme edema, oxidative stress and inflammation. For instance, too early intracoronary transfer of bone-marrow-derived stem cells very probably contribute to the failure of Janssens's trial [4], where stem cells were given only 24 hours after STEMI onset. Too late cell transfer may diminish engraftment and survival of stem cells because of a lack of chemotactic and growth factors in the infarction area, and the valuable time is lost for the attenuation of beneficial paracrine effect of these cells on reperfusion injury and local inflammation. Higher number of stem cells and repeated cell therapy might be required for substantial benefit in the process of myocardial reparation. Selection of patient may be crucial. Patients with small infarctions do not need any regeneration support because they have no any significant remodelling after infarction. On the other side, in patients with huge STEMI, it is hard to believe that one intracoronary application on stem cells can permanently improve cardiac function at the level of clinical relevance. The results of stem cell trafficking after intracoronary application have showed that a small number of cells are sited in the infarction area several hours after [9], and that direct intramyocardial injections of stem cells via transendocardial route using electromechanical guidance might be a better way for cell delivery [10].

The most often used primary endpoint in the stem cell trial in acute STEMI was the change of LVEF during follow-up (mostly the period of 4-6 months). The standard variation of this endpoint was much larger in experimental groups than in controls in almost all studies published till now, which means that some patients have probably the benefit of stem cell therapy, white some even harmful effect of it. Unfortunately, these modifying factors for the outcome of stem cell therapy after MI are mainly unknown.

Primary endpoints were the increase of LVEF (measured by echocardiography) and decrease of infarction size (measured by myocardial perfusion scintigraphy) by 5% (both parameters) using intracoronary injections of autologous bone-marrow-derived MNC in 7–14 days after huge, reperfused STEMI involving major branches of left coronary arteries as the culprit vessels. Secondary endpoint of the study was a reduction of major adverse cardiac events (MACE) during follow-up of at least 2 years. Also, the aim of this study was to determine factors which influence the efficacy of MNC therapy for myocardial regeneration in the subacute phase of large STEMI.

Methods

The study was a non-randomized, open, single centre study, in which the experimental group was compared with the well-matched control group. All consecutive patients with the eligible inclusion criteria, admitted in the Clinic of Emergency Internal Medicine, Military Medical Academy, Belgrade, Serbia, in a 5-year period (February 2004 to February 2009) were enrolled in this study. The study was approved by the local Ethics Committee of the institution and a written informed consent was obtained from all participating patients.

Inclusion criteria for intracoronary bone-marrow-derived MNC injections were the first large STEMI at the territory of the left coronary artery, age between 18 and 71 years, LVEF between 24 and 41% measured on the fifth day from the infarction, the absence of previously known cardiac disease that could influence the myocardial function before STEMI, and the successful reperfusion either by percutaneous coronary intervention (PCI) or with fibrinolysis during the first 2–12 hours from the pain onset. The patients with electrocardiography (ECG) signs of a successful reperfusion (resolution of ST segment elevation for more than 50% in the ECG lead with the highest ST elevation at admission) at the 90 minutes from the start of fibrinolysis had successful PCI in 48 hours from admission. The patients with no early ECG signs of reperfusion were submitted to rescue PCI immediately after failed fibrinolysis. The main exclusion criteria were the presence of any chronic inflammatory or malignant disease, nonresponsiveness to clopidogrel at the fifth day of STEMI, and allergy on either aspirin or clopidogrel. The responsiveness to clopidogrel was determined by platelet ag-

gregometry on adenosine diphosphate (ADP), and it was added to exclusion criteria during the study, when one patient had stent thrombosis several days after discharge in whom we confirmed the resistance to clopidogrel therapy after that event. The control group included the patients with the same inclusion and exclusion criteria as the study group with no cell therapy because of technical reasons (9 patients) and the part of them were a historical control group – 15 patients treated before introduction of cell therapy in our institution between 2000 and 2003.

Bone marrow harvest and cell processing and implantation

We harvested bone marrow 7–14 days after STEMI, under general anesthesia. The target volume of bone marrow was 250 mL. Bone marrow was filtered and processed to get cell suspension enriched with MNC (40–50% of all nuclear cells) with lower hematocrit (Ht) (Ht target less than 0.3) and platelet number (less than 100 000/microliter). Cell viability was estimated by trypan-blue test, and it was always above 95%.

The final volume of 160 mL of resuspended cells was infused into the left main coronary artery as slow - 2 minutes boluses of 20 mL, with the one-minute pause between, through the diagnostic catheter.

Echocardiography examination

Transthoracic echocardiography examination was performed between 5 and 7 days and at the fifth month after MI. Simpson biplane method was used for the determination of LVEF.

Myocardial scintigraphy

Single photon emission computed tomography was done between 5 and 9 days after STEMI and in the fifth month. The first examination was the rest scintigraphy only using Tc99m-MIBI (740 MBq) and the second one was performed in stress (Tc99m-MIBI 370 MBq) and 3 hours later in rest (Tc99m-MIBI 740 MBq). Stress was induced as a "hybrid protocol" using adenosine 140 μg/kg/min intravenously for 4 minutes together with low level exercise – 25-50 W on the ergometry bicycle. Segmental model technique using 20 segments of myocardium (AutoQuant software, Cedars-Sinai QPS/QGS component of AutoQuant) was used to determine the size of perfusion defect. All segments with the tracer uptake lesser than 50% than normal were considered nonviable.

Biochemical analysis

Admission serum glucose level was measured by the standard hexokinase-glucose-6-phosphate dehydrogenase method (Dade Behring XPAND, Germany). C-rective protein (CRP) was measured daily in 1-3 days after MI by the immunonephelometric method (BNTM II System, Dade Behring, Germany) and the highest level was included in the analysis. The cardiac-specific isoenzyme of creatine kinase (CK-MB) and LDH serum levels were determined every 6 hours after the admission for 3 days by standard tests (Dade Behring XPAND, Germany).

Patient follow-up

All the patients in both groups were clinically examined after 1, 4 and 6 months with echocardiography and SPECT examination in the fifth month. All the patients also submitted to adenosine-exercise stress testing after 4 months from infarction.

Routine coronarography performed in all the patients in the cell therapy group, and ischemia-driven (typical chest pain inside 6 months from the infarction or positive ischemia on SPECT) coronarography performed in the control patients.

After six months the patients were examined routinely every six months and all other diagnostic measures were taken depending on symptoms.

Statistical analysis

Sample size calculation was based on the expectation that a treatment difference in primary endpoints would be 4% with SD of 5% between the experimental and the control group, indicated that at least 26 should have been enrolled in each group with 0.05 two-sided significance and 90% power.

Discrete variables are reported as counts (percentages), and continuous variables as mean ± SD (if data were normally distributed), or median with interquartile range (IQR) if data were skewed). Baseline characteristics of patients, endpoints and MACE, were compared between groups with the chi-square test for discrete variables. Differences between groups for continuous variables with normal distribution compared with Student *t* test and if it is not normally distributed with Mann-Whitney *U* test. A value of $p < 0.05$ was considered statistically significant.

Results

The cell therapy group included 19 patients and the control group 24 patients. One patient in the cell therapy group had early stent thrombosis (seven days from the discharge). In that patient we found poor platelet response to ADP (platelet aggregability to ADP was more than 50% during the maintenance dual antiaggregatory therapy) and excluded him from further study. There were no significant differences between baseline patient characteristics which we consider important for the study results, except that the patients from the control group had higher frequency of hypertension, and the cell therapy group patients received borderline significant longer stents cover on infarct-related lesion than the control (Table 1). However, we think that these differences had no influence upon the main results of our study.

Both baseline and a 4-month infarction size and LVEF were similar in the groups (Table 2). However, patients in the cell therapy group had greater decrease in infarction size measured by myocardial perfusion scintigraphy, but this did not result into the greater increase of LVEF in the cell therapy group as compared with the controls (Table 2).

Nine of 18 patients in the cell therapy group and 7 out of 24 patients in the control group had ΔLVEF greater than 5% after 4 months ($p = 0.210$) (Table 3). Inside the experi-

Table 1

Characteristics of the patients

Patients' Characteristics	Group of patients: cell therapy (n = 18)	Group of patients: control (n = 24)	*p*
Age (years; $\bar{x}$ ± SD)	50 ± 10	56 ± 11	
Males, [n(%)]	15 (83.3)	22 (90.1)	
Risk factors (n)			
smoking	11	12	
hypertension	7	19	0.017
hypercholesterolemia	10	12	
diabetes mellitus	2	3	
Infarction-related artery (n)			
LAD artery	17	21	
ACX	1	3	
Reperfusion therapy (n)			
primary PCI	10	15	
rescue or urgent PCI after fibrinolysis	8	9	
Stenting (n)	13	20	
Average stent length (mm, median [IQR])	23 (19-28)	16(14-26)	0.053
TIMI flow 3 after PCI (n)	14	20	
TIMI flow 2 after PCI (n)	2	4	
Time from pain onset to reperfusion (h, median [IQR])	4.0 (2.25-7.5)	4.0(2.12-8.75)	
Therapy at discharge (n)			
aspirin	18	24	
clopidogrel	18	24	
carvedilol or bisoprolol	18	22	
ACE inhibitor	16	20	
statins	15	20	

LAD – left anterior descending, ACX – circumflex artery, PCI – percutaneous coronary intervention, TIMI – thrombolysis in myocardial infarction, IQR – interquartile range, ACE – angiotensin – converting enzyme

Table 2

Left ventricle ejection fraction and myocardial infarction size at baseline and at a 4 month follow-up

Parameters (%, median [IQR])	Group of patients: Cell therapy (n = 18)	Group of patients: Control (n = 24)	*p*
Baseline infarction size	29.0 (25.7-35.3)	29.0 (26.7-33.7)	
Six months infarction size	26.0 (19.7-33.0)	27.0 (22.3-32.0)	
Delta infarction size	-4.50± (2.0-9.0)	-3.00 (1.0-4.0)	0.020
Baseline LVEF	34.5 (31.5-35.0)	35.0 (33.5-37.0)	
Six months LVEF	37.0 (32.7-43.7)	38.0 (35.0-42.0)	
Delta LVEF	4.0 (0.0-8.5)	3.0 (-0.7-6.0)	

LVEF – left ventricular ejection fraction; IQR – interquartile range

Table 3

Factors that could influence the improvement of left ventricular ejection fraction (LVEF) in the patients with cell therapy and the control group

	Cell therapy group (n = 18)			Control group (n = 24)		
	ΔLVEF > 5.1% (n = 9)	ΔLVEF < 5.1% (n = 9)	*p*	ΔLVEF > 5.1% (n = 7)	ΔLVEF < 5.1% (n = 17)	*p*
Age (years; median [IQR])	53 (50-59)	46 (39-58)	0.234	59 (50-65)	53 (46-67)	0.951
Time pain/reperfusion (h; median [IQR])	3.5 (2.0-7.2)	4.0 (3.2-9.7)	0.382	4.0 (1.5-9.0)	4.0 (2.7-8.5)	0.576
Glycemia at admission (mmol/L, median [IQR])	7.5 (6.8-19.1)	7.3 (5.5-8.1)	0.534	8.9 (8.0-9.0)	8.0 (7.1-10.7)	0.671
CRP at 48 h (mg/L, median [IQR])	45.8 (17.2-69.8)	49.2 (6.5-52.0)	0.798	45.9 (29.7-93.5)	37.7 (17.4-86.0)	0.548
LDH maximum (IU/L, mean ± SD)	1689 ± 139	2133 ± 215	< 0.001	1945 ± 402	2369 ± 872	0.236
Baseline LVEF (%, median [IQR])	35.0 (33.2-38.0)	31.0 (30.0-34.7)	0.065	35.0 (34.0-36.0)	35.0 (32.5-37.5)	0.576
Baseline MI size (%, mean ± SD)	26.7 ± 5.2	34.9 ± 3.7	0.001	27.0 ± 2.8	30.2 ± 5.60	0.448
Number of MNC injected ($n \times 10^8$/L; mean ± SD)	4.2 (2.1-6.9)	6.2 (3.8-10.8)	0.234	–	–	–

IQR – interquartile rang; CRP – C-reactive protein; LDH – lactate dehydrogenase; MI – myocardial infarct; MNC – mononuclear cells

mental group we compared presumable important variables which might influence the outcome of MNC therapy. There was no difference in age, time from the pain onset to reperfusion, glycemia on admission, maximum level of CRP after STEMI, and the number of injected MNC between the group with and the group without a significant improvement of LVEF and a decrease of infarction size, both prespecified as 5%. The patients with an improvement in LVEF more than 5% had significantly lower maximal LDH levels ($p < 0.001$) and smaller baseline infarction size ($p = 0.001$) than the group with a treatment failure (Figure 1). In the control group there were no significant differences for all variables between those who had a significant improvement of LVEF as compared with the patients with no such improvement.

There was no difference in MACE between the two groups (Table 4).

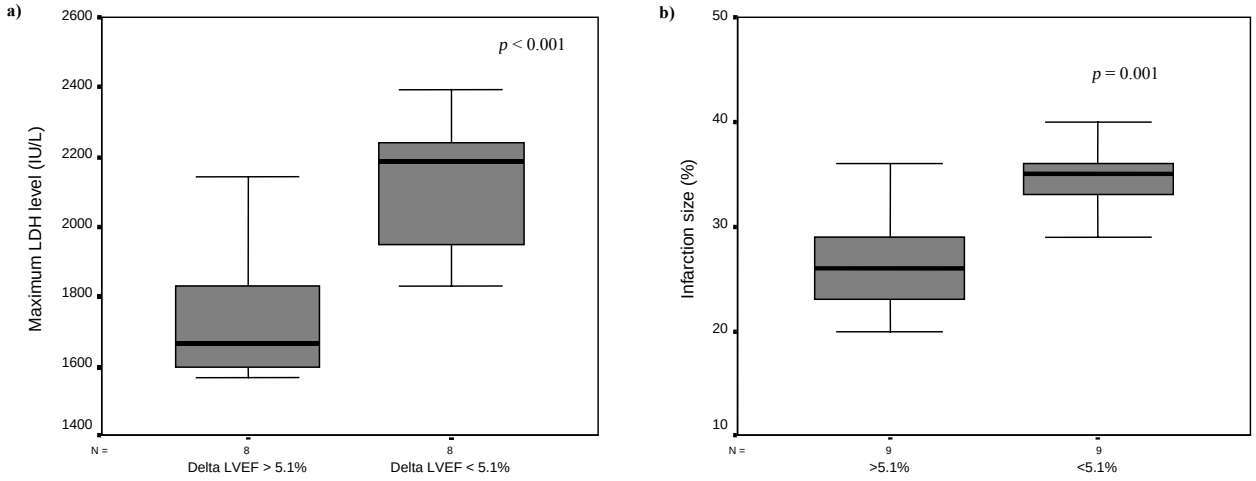

Fig. 1 – (a) Maximum lactate dehydrogenase (LDH) levels and (b) baseline infarction size according to a significant improvement of left ventricular ejection fracion (LVEF) after 4 months

Table 4

Major adverse cardiac events (MACE) during follow-up (from 6 months to 5 years)

MACE	Group of patients	
	cell therapy (n = 18)	control group (n = 24)
Restenosis [n(%)]	7 (38.9)	7 (29.2)
TVR [n(%)]	5 (27.8)	6 (25.0)
Coronary death [n(%)]	0 (0.0)	2 (8.3)
Hospitalization for heart failure [n(%)]	0 (0.0)	4 (16.7)
*Composite of death, TVR and heart failure [n(%)]	5 (27.8)	11 (45.8)

TVR – target vessel revascularization; *hierachical composite (when a patient who had died have submitted to TVR or had heart failure, he was counted only once).

Discussion

The main result of this study was that the patients with too large infarction measured by the maximum LDH release had no benefit of intracoronary MNC infusion in the subacute phase of large STEMI. In two large randomized trials REPAIR-AMI [1] and REGENT [6] the patients with baseline LVEF lower than median had greater increase in LVEF after a 6-month follow-up. However, median values of baseline LVEF in those two studies were 48.9% and 37% and that were much higher than median value in our study. The question is what baseline LVEF is optimal for the cell therapy. But, when we consider this question one more thing must be included, and that is the timing of a baseline LVEF estimation. If it is estimated too early, the influence of stunning may be too strong and patients with viable but severely stunned myocardium would be submitted to cell therapy. In our study "inclusion" of LVEF measurement were done 5-7 days after STEMI, in attempt to avoid a strong influence of inevitable stunning on LVEF. That was unlike to large randomized studies [2–5] where recruitment of patients did not include the baseline LVEF at all, or the inclusion-baseline measurement of LVEF was performed earlier in the course of STEMI [1, 6]. The studies using magnetic resonance imaging (MRI) estimation of LVEF and left ventricle volumes had a somehow opposite problem, because a baseline MRI was performed in days, or even weeks after intracoronary transfer of stem cells [5, 6] when some effects of stem cells may already present and it would be diminished in such approach. The second question about using LVEF as a primary endpoint is if we need some other more sophisticated, but simple parameters for the initial recruitment and follow-up of patients. The change in global LVEF is probably a too rough surrogate endpoint for the estimation of efficacy in stem cell ther-

apy studies at this stage of investigation. Serial regional changes in systolic and diastolic function in the infarction zone especially during exercise or pharmacological stress are probably better tool for the estimation of stem cell therapy after STEMI. Some other more sophisticated echocardiography methods like myocardial strain or some parameters of diastolic function had even better prognostic value for patients with severely damaged myocardium [11, 12].

Our results also showed that maximum lactate dehydrogenase (LDH) levels and the baseline infarction size measured by single photon emission computed tomography (SPECT) were good predictors for the success/failure of intracoronary mononuclear cell (MNC) therapy. The patients with too large increase in LDH and too large infarction area on SPECT did not have benefit of MNC therapy after STEMI. The reason for that may be that maximum LDH level after myocardial infarct (MI) mirrored two important partly connected events: necrosis (release of LDH from the necrotic cardiomyocites) and reperfusion injury (release of LDH by the activated leukocytes in the infarction zone), and both of them can influence the outcome of cell therapy after MI. It is interesting that CRP level was not different between the patients with and without benefit of cell therapy. It may be that a systemic inflammatory response after infarction depends on the size of infarction but also on the presence of heart failure and specific, individual immunogenic reaction to injury, and the correlation between necrosis quantum and CRP levels is only partial. However, the role of CRP in myocardial reparation process may be more direct. In a recently published study, Turan at al. [13] found that patients with higher CRP levels after infarction have decreased mobilization of bone-marrow-derived stem cells. According to our and Turan's results, it seems that a higher systemic inflammatory response can influence the mobilization of stem cells to blood – natural regeneration process, but do not impair a positive effect on cardiac remodelling of the intracoronary stem cell implantation. As far as we know, there is no such study which connects any biomarker to the outcome of the cell therapy after STEMI.

Age was not an important factor for the prediction of LVEF increase or infarction size decrease after MNC implantation in our study. Although an advanced age can lower the mobilization of stem cells after infarction [13] and decrease angiogenic capacity of stem cells [8], we found the opposite, i.e. the patients with a significant improvement of LVEF tended to be older (not significantly). The explanation for that is, maybe, a longer duration of coronary disease with more developed collaterals which may be important for the deliverability and engraftment of stem cells in the infarction area.

It should be logically that a higher number of intracoronary injected stem cells means the better results for regenerative cell therapy after STEMI. However, REGENT [6], as well as our trial, found no correlation between LVEF improvement and the number of bone-marrow-derived cells injected intracoronary. There is, maybe, a saturation level for the number of stem cell engraftment in the infarction area for one occasion in the short time of delivery. The results of Yao et al [14], show that the patients treated with repeated intracoronary implantation of bone-marrow-derived stem cells, first in 3-7 days after STEMI and then 3 months later, had larger increase of LVEF than patients in whom cell therapy was done only once in the subacute phase of STEMI.

The longer time from the pain onset to the primary PCI was reported to be a significant predictor for the improvement of LVEF after a stem cell therapy. We found no such dependence, and the reason for that was that all the patients in the REGENT trial were treated by primary PCI and the exact time of reperfusion was precisely known, and in our study almost a half of patients received fibrinolytic therapy first and the timing of reperfusion in those patients were estimated approximately by the timing of electrocardiogram changes typical for reperfusion.

The second, but very important, result of our study was that MACE tended to be higher in the control group than in the stem cell group. The only trial that published a reduced MACE rate after a year of intracoronary stem cell therapy after STEMI was the largest REPEAR-AMI [15] trial.

The main limitation of this preliminary study was its non-randomized character but we tried to avoid that with a well-matched control group. A small number of patients is the second huge limitation, but that number of patients enrolled was the maximum achievement for our institution during a 5-year study. The two largest trials of bone-marrow-derived stem cell therapy show that the patients treated with intracoronary transfer of MNC or their CD34+CXC4R+ subpopulation in the second week of a successfully reperfused STEMI have a significant improvement of LVEF only if they have a baseline LVEF lower than median values for these studies. On the contrary, the results of our study open the question of the lowest limit of baseline myocardial damage.

Conclusion

According to our results, the patients with extremely large infarction, estimated by infarction scintigraphy size and the maximum increase of LDH, have no benefit of intracoronary MNC transfer as compared with the patients with lesser, but severe degree of myocardial damage. We suppose that the STEMI patients with relatively narrow range of baseline infarction size or LVEF between 25 - 40% may have some benefit of early treatment with bone-marrow-derived MNC.

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