CLINICAL STUDY

Intracoronary injection of autologous bone marrow-derived mononuclear cells in patients with large anterior acute myocardial infarction and left ventricular dysfunction: A 24-month follow up study

Skalicka H1, Horak J1, Kobylka P2, Palecek T1, Lihnart A1, Aschermann M1

2nd Department of Internal Medicine, General University Hospital in Prague, Czech Republic.

skaldah@seznam.cz

Abstract: Objective and background: Despite the use of reperfusion therapies, outcomes in patients with large myocardial infarction (MI), late reperfusion and left ventricular (LV) dysfunction are poor. We investigated long-term safety and efficacy of intracoronary injections of autologous bone marrow-derived mononuclear cells (BMNCs).

Methods: 27 patients with anterior MI (age 59±12 years, mean baseline LV ejection fraction (LVEF) 39±5 %), who underwent percutaneous coronary intervention 4–24 hours after the onset of symptoms, were randomly assigned either to intracoronary BMNCs injection (n=17, BMNCs group, out of which 14 underwent long-term follow-up), or to standard therapy (n=10, Control group). The LVEF, the LV end-diastolic and end-systolic volumes (LVEDV, LVESV) were assessed by echocardiography at discharge, Month 4 and 24. Myocardial perfusion was assessed using SPECT at baseline and Month 4.

Results: At 24-month, there was no difference in rates of serious clinical events (36 % vs 50 %, p=0.54). At Month 4 LVEF improved to similar extent in both groups (absolute change +5.8 % vs +7.6 %, p=0.75), with similar infarct size reductions (−10.9 % vs −12.2 %, p=0.47). However, at Month 24, LVEF further improved in BMNCs patients (+12 % vs +8.5 %, p=0.03). This effect resulted from a more pronounced reduction in LVESV (−2.6 ml vs −1.8 ml, p=0.26) and a smaller increase in LVEDV (+16.7 ml vs +17.9 ml, p=0.27) suggesting beneficial long-term effects on LV remodeling.

Conclusions: BMNCs injections in patients with MI and LV dysfunction were associated with a significant improvement of global LVEF during long term follow-up compared to standard therapy (Tab. 3, Fig. 1, Ref. 50).

Key words: bone marrow-derived mononuclear cells, myocardial infarction, remodeling, left ventricular ejection fraction.

Currently, up to 30 % of patients with ST segment elevation myocardial infarction, usually those presenting later, show ongoing left ventricular (LV) remodeling with poor clinical outcomes, despite primary percutaneous coronary intervention (PCI) (1, 2). Cardiac transfer of bone marrow-derived stem and progenitor cells has been investigated as an adjunctive therapy to promote regeneration of the infarcted myocardium (3–5). Pilot clinical studies suggested that infusion of bone marrow or progenitor cells into the infarct-related coronary artery is feasible and may enhance recovery of the LV contractile function (6, 7). However, in randomized trials, the effects of BMNCs on LVEF and remodeling were controversial (8–11), some studies reporting enhanced recovery of LVEF (12–14), which was not confirmed in other studies (11, 14). Since the LVEF reduction remains the major predictor of a poor outcome even in the era of PCI (15), enhanced recovery of the LV contractile function resulting from the bone marrow cells implantation might be beneficial especially in patients with large infarctions. Therefore, we designed a randomized study to assess the safety and efficacy of intracoronary injection of autologous BMNCs in patients with large acute anterior myocardial infarctions who presented late and who were successfully treated with primary PCI. The short-term results of our study were not encouraging (16), showing no additional effects of the cellular therapy on the left ventricular function compared to the standard treatment, and lead to early termination of the study. However, little is known about potential long-term effects of this treatment modality. This report presents the results of the 24-month follow up study in our patients.

Methods

Patients
The study population consisted of 27 consecutive patients (age 59±12 yrs; 81 % were males, the mean baseline LVEF was
39±5 %, range 19–45 %) with their first ST-segment elevation acute anterior myocardial infarction resulting from occlusion of the proximal left anterior descending coronary artery (LAD) and with TIMI flow grades 0-1 at presentation, who were successfully treated with primary PCI with stent implantation. The patients were eligible for the study provided they had undergone the primary PCI 4 to 24 hours after the onset of symptoms and their echocardiogram performed 24 hours after the PCI procedure confirmed reduced LVEF (LVEF ≤50 %) with at least 3 akinetic segments in the LAD perfusion territory. The following were the exclusion criteria: age ≥80 years, severe multivessel coronary artery disease requiring surgery, wall motion abnormalities in non-LAD territory, serious renal or hepatic disease, blood cells disorders, documented cancer or terminal illness. The study protocol was approved by Medical Ethical Committees of all the involved institutions and informed consents were obtained from all patients included in the study. The eligible patients were randomly, at a 2:1 ratio, assigned either to a group with intracoronary BMNCs injection 4 to 11 days after PCI (BMNCs group) or to a standard medical therapy group (Control group). No bone marrow aspirations or sham injections were performed in the control group.

Protocol
The LV ejection fraction and volumes were assessed on echocardiography at discharge, at Month 4 and Month 24. In order to allow for recovery of the stunned myocardium, echocardiographic examinations performed at discharge served as baseline measurements for comparison with the follow-up echocardiographic examinations. Myocardial perfusion and glucose uptake was assessed by single photon emission computed tomography (SPECT) at patients discharge and at Month 4, using technetium-99m tetrofosmin and F18-fluorodeoxyglucose. Coronary angiography was repeated at Month 4. Cardiac troponin I, creatine kinase (CK) and its isoenzyme (CK-MB), as well as the white blood cell count and C-reactive protein levels were assessed before and serially after the BMNCs transfer and at Month 4. In addition, Holter monitoring was performed before and after the BMNCs transplantation, at Month 1 and Month 4. The quality of life was assessed at Month 24 using a standard SF-36 questionnaire.

BMNCs isolation and intracoronary injections (Fig. 1)
In the BMNCs group, aspiration of BMNCs was performed by a staff hematologist 4 to 11 days after the index PCI. Bone marrow (BM) was harvested from the posterior superior iliac crest through multiple aspirations under analgesia sedation. Each BM aspiration was performed using a pre-filled syringe containing 1ml of an anticoagulant, to which 3ml of the bone marrow were harvested. The aspirates were transferred into the Bone Marrow Collection Kit with a Pre-Filter and Inline Filters (Baxter R4R2107, USA) and further processed in a closed blood bag system. Erythrocytes were separated through sedimentation with Gelofusine (Braun Melsungen, Germany) in the closed blood bag system. After the BMNCs isolation, the remaining plasma was removed, producing a BMNCs concentrate. The final BMNCs preparation was immediately transferred to a cath lab for intracoronary injection. The number of CD34+ cells was determined by a flow cytometry...
Tab. 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>BMNCs group (n=17)</th>
<th>Control group (n=10)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>12 (71)</td>
<td>10 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years</td>
<td>61±14</td>
<td>54±10</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>5 (30%)</td>
<td>6 (60%)</td>
<td>NS</td>
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<tr>
<td>Smokers, n (%)</td>
<td>11 (66)</td>
<td>9 (90%)</td>
<td>NS</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (29)</td>
<td>2 (20)</td>
<td>NS</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>7 (42%)</td>
<td>6 (60%)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial blood pressure, baseline (mmHg)</td>
<td>129±33</td>
<td>142±21</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic arterial blood pressure, baseline (mmHg)</td>
<td>77±18</td>
<td>82±21</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, baseline (bpm)</td>
<td>83±19</td>
<td>78±10</td>
<td>NS</td>
</tr>
<tr>
<td>Extent of CAD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SVD, n (%)</td>
<td>7 (41)</td>
<td>6 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>MVD, n (%)</td>
<td>10 (59)</td>
<td>4 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Time from the onset of pain to PCI, (min)</td>
<td>315 (range 300–660)</td>
<td>330 (range 300–630)</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum creatine kinase (ukat/l)</td>
<td>59±12</td>
<td>35±17</td>
<td>NS</td>
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<tr>
<td>Maximum troponin (ug/l)</td>
<td>152±22</td>
<td>147±20</td>
<td>NS</td>
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<td>Killip class</td>
<td></td>
<td></td>
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<tr>
<td>I/II, n (%)</td>
<td>15 (88)</td>
<td>9 (90)</td>
<td>NS</td>
</tr>
<tr>
<td>III/IV, n (%)</td>
<td>2 (12)</td>
<td>1 (10)</td>
<td>NS</td>
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<td>TIMI flow after PCI</td>
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<td>Grade 2, n (%)</td>
<td>4 (23)</td>
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<td>Grade 3, n (%)</td>
<td>13 (77)</td>
<td>8 (80)</td>
<td>NS</td>
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<tr>
<td>Catecholamines, n (%)</td>
<td>2 (12)</td>
<td>1 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>39±7</td>
<td>39±4</td>
<td>NS</td>
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<tr>
<td>Medication after PCI</td>
<td></td>
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<td></td>
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<tr>
<td>Aspirin, n (%)</td>
<td>17 (100)</td>
<td>10 (100)</td>
<td>NS</td>
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<td>Clopidogrel, n (%)</td>
<td>17 (100)</td>
<td>10 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors/ AT1 blockers, n (%)</td>
<td>13 (76)</td>
<td>8 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>14 (76)</td>
<td>10 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>15 (88)</td>
<td>10 (100)</td>
<td>NS</td>
</tr>
</tbody>
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Abbreviations BMNCs = bone marrow-derived mononuclear cells, CAD = coronary artery disease, MVD = multivessel disease, PCI = percutaneous coronary intervention, SVD = single vessel disease, ACE inhibitors = angiotensin converting enzyme inhibitors

Analysis. Intracoronary transplantation of BMNCs was performed on the day of the harvest, as described above (6). In brief, 4 to 6ml portions of the BMNCs suspension were injected into the LAD through a central lumen of an inflated over-the-wire balloon catheter. Low-pressure balloon inflations were performed within the stented segment for up to 3 minutes or up to the maximum tolerated time, and were followed by 3minute reperfusions. This step was repeated 5 to 7 times, depending on the BMNCs suspension volume.

Echocardiography

All the studies were performed with a commercially available system (Vivid 7, Vingmed-General Electric, Horten, Norway). The LV volumes (end-diastolic and end-systolic) and ejection fractions were assessed on apical 4-chamber and 2-chamber views using the biplane Simpson’s method, the dimensions were measured along a standard parasternal long axis (17). All studies were stored in a digital (raw data) format, as well as on a S-VHS videotape for an off-line analysis. All the measurement data were the mean values of the data obtained for three consecutive beats. Digital baseline and follow-up echocardiographic recording were analyzed by echocardiography specialists blinded to the patient group assignment.

Assessment of myocardial viability by SPECT

Technetium-99m sestamibi (600 MBq) was injected intravenously to evaluate rest perfusion. After an intravenous injection of glucose and insulin (0.2 g of 40 % glucose solution and 0.2 units of short-acting insulin), F18-fluorodeoxyglucose (400 MBq) was injected intravenously to assess myocardial glucose uptake. Dual-isotope simultaneous image acquisition was performed 60 minutes after the F18-fluorodeoxyglucose injection, using high-energy 511-keV collimators. A symmetrical 15 % energy window was preset on each side of the 140-keV photon peak of technetium-99m sestamibi and 511-keV photon peak of F18-fluorodeoxyglucose. The data were acquired over 180° and stored in a 64x64 computer matrix. The images were displayed in polar maps, which were normalized to a maximum activity (set at 100 %). To assess myocardial viability, the polar maps were divided into 16 segments (17). Segments with normal technetium-99m tetrofosmin myocardial perfusion and segments with perfusion defects but preserved or increased F18-fluorodeoxyglucose (perfusion-metabolism mismatch) perfusion were considered viable. Segments with a match (concurrently reduced perfusion and metabolism) were considered unviable.

Statistical analysis

Clinical results were analyzed based on the intention-to-treat principle. The continuous data are presented as the mean ± standard deviation or the median and the interquartile range. The categorical data are presented as counts and percentages. The two-sided paired and unpaired Student’s t-test or the Fisher’s exact test were
On average, 171±48 ml of bone marrow blood was harvested and harvested and intracoronary injection was 9 days (range, 4 to 11). The viability of BMNCs ranged from 94 to 99 %. The median total time of ischemia during repeated intracoronary BMNCs (n=17) or the control (n=10) group.

Results

Baseline characteristics

A total of 27 patients were randomly assigned to either the BMNCs (n=17) or the control (n=10) group. Table 1 shows the baseline characteristics in both groups. The median time from the onset of pain to PCI was more than 5 hours. The majority of patients (89 %) were in the Killip I and II class at admission. The BMNCs group of patients were significantly older and had a slightly higher prevalence of multivessel coronary artery disease than the controls. Other baseline characteristics including a degree of LV dysfunction were comparable between both groups. Similar percentages of patients in both groups showed the TIMI flow grade 3 after their PCI. The median time from PCI to the bone marrow harvest and intracoronary injection was 9 days (range, 4 to 11).

Functional outcome

Table 2 shows baseline, Month 4 and Month 24 echocardiographic indices of the LV systolic function, the LV volumes and diameters according to the treatment assignment. LVEF improved to a similar extent in both groups at Month 4 (the absolute change was +5.8 % in the BMNCs group vs +7.6 % in the control group, the relative change was +15 % vs +19 %, p=0.75). Similarly, at Month 4, the infarction size was reduced to the same extent (the relative change was minus 26.3 % vs minus 25.7 %, p=0.47) in both groups. However, at Month 24, the left ventricular function continued to improve significantly in the BMNCs patients (the absolute change from the baseline was +12 %, the relative change was +31 %), while there was no further change in the control group (the absolute change was +8.5 %, the relative change was +21 %, p=0.03). This effect resulted from a more pronounced decrease in LVESV (the absolute change was -2.6 ml vs –1.8 ml, the relative change was -2.65 % vs –1.80 %, p=0.26) with a minor change in LVEDV (the absolute change was +0.3 mm vs +2.8 mm, the relative change was +0.7 % vs +7.5 %, p=0.09) and a smaller increase in LVEDD (the absolute change was +5.8 mm vs +7.6 mm, the relative change was +10 % vs +19 %, p=0.16) and no change in LVESD (the absolute change was +0.7 % vs +8.5 %, p=0.27) in the BMNCs group, suggesting a possible beneficial long-term effect on LV remodeling.
The intracoronary BMNCs transfer was successful in all the enrolled patients. During the 24-month follow up, no significant difference was observed in the rates of serious clinical events between both groups (6 patients in the BMNCs group (36 %) vs. 5 patients (50 %) in the control group, p=0.54). Two patients developed serious complications before the cell transfer, which ultimately resulted in death. One patient had a ventricular septal rupture prior to the BMNCs harvest and was urgently operated. She died 3 months later because of severe heart failure. The other patient suffered from stent thrombosis with reinfarction before the BMNCs transfer. He underwent a complicated PCI procedure followed by CABG, and died of sepsis and ARDS 2 weeks later. Early during the follow up period, 6 weeks after the BMNCs transfer, inoperable biliary carcinoma was diagnosed in 1 patient (asymptomatic at the time of index myocardial infarction) who died 2 months later. There was no difference in restenosis rates at Month 4 and in rates of late ischemic events, as well as in rates of late revascularization (4 patients in both groups). At Month 24, the mean NYHA class was better in the treated group (1.2±0.42 vs. 1.9±0.83, p=0.04), however, there were no significant differences in QOL SF 36 parameters between the groups.

Discussion

This randomized study evaluated safety and efficacy of intracoronary injections of autologous BMNCs in patients with large acute anterior myocardial infarction and late presentation, who were successfully treated with primary PCI. Despite the prior successful PCI of the infarct-related artery, such patients are at greatest risk of unfavorable post-infarction LV remodeling, which is a major cause of late, infarct-related heart failure events and death (18). The principal outcome of this study is the finding that although at Month 4 the intracoronary infusion of BMNCs did not appear to enhance recovery of the LVEF nor to reduce the LV volumes and the infarction size in the treatment group , compared to the control group, the long-term follow up analysis of the LV function demonstrated favorable changes in the BMNCs group, including a more pronounced decrease in LVESV and reduced LV dilatation, which resulted in significant ejection fraction improvements. These findings suggest a possible long-term beneficial effect on the LV remodeling.

Clinical effects of BMNCs in acute myocardial infarction

The possibility of improved myocardium regeneration and improvement of its function after the SCs application has been demonstrated in a number of experimental settings on various animal models (5, 19–22). Early, non-randomised clinical studies showed enhanced recovery of the LV contractile function after intracoronary infusion of BMNCs (23–26). However, results of randomised studies are more controversial. Whereas some studies showed a minor positive effect on recovery of the LV contractile function (6, 27–29), other studies failed to confirm these results (11, 30). Similarly, there were no consistent outcomes to demonstrate infarction size reduction effects (9, 30–32). In the largest study so far (33), patients assigned to the BMNSc group showed a moderate, but significant gain in the LV ejection fraction, compared to the controls. The results and conclusions of these studies are difficult to interpret, because of heterogeneity of the patient populations and the study designs used. The meta-analysis by Martin-Randon et al (34) can be considered the most comprehensive summary of all important studies with intracoronary BMNCs implantation in AMI patients. Only larger randomized studies with similar study designs were included (13 studies, with a total of 811 patients involved). The median follow up time was 4 months. Two substantial results arise from this analysis: 1. intracoronary application of BMSCs in patients with ST-segment elevation myocardial infarction is safe. The combined clinical indicator including rates of deaths, rates of re-infarctions, hospitalisations due to heart failure and the need for revascularisation were similar between the actively treated groups and the controls and there were no records of higher rates of arrhythmias in patients who were given BMSCs. 2. Administration of BMSCs results in a moderate, but statistically significant LV systolic ejection fraction improvement by 2.99 % (p = 0.0007). Furthermore, a significant decrease in the left ventricular end-systolic volume by 4.74 ml (p = 0.003) was demonstrated at the same time. A minor, insignificant decrease in the end-diastolic volume by 2.47 ml (p = 0.13) also occurred. Compared to the control group, reduction in the infarction size by 3.51 %, was detected on SPECT. This was consistent with a previous meta-analysis of all studies, dealing with stem cells implantations in various cardiac clinical indications (14) , as well as with a prior meta-analysis by Lipinski et al (35).

Long-term results of the BMNCs therapy

There are limited data on the long-term effects of the BMNCs therapy. According to one randomised study (36), initial positive effects on the LV function in the actively treated group receded in 18 months. In another study, after two years, the clinical course in terms of rates of hospitalisations for heart failure appeared better in patients who underwent intracoronary cell implantation (33). In
a recent publication (37), analyzing long-term effects of the BMNCs transfer after MI in 62 patients, global as well as regional LV function was significantly improved at 12 months and a significant improvement was observed even after 5 years, while the LV function deteriorated in a non-randomised control group of 62 patients, who refused the procedure. This was consistent with a marked decrease of the infarction size in the treated patients, compared to the controls. Most interestingly, after almost 5 years of the follow-up, mortality was significantly lower in the treatment group. This is the first evidence that an initial functional effect of the BMNCs transfer could translate into a long-term benefit in hard clinical endpoints. The authors speculate that the above effects could result from decreased occurrence of heart failure through prevention of LV remodeling, as well as from lower incidence of arrhythmias, suggested by improvements in the heart rate variability and lower incidence of late potentials. In our study, the treatment group patients, although slightly disadvantaged by their older age and higher multi-vessel disease incidence rates, showed a tendency towards a lower incidence of the combined clinical endpoint, and a better subjective status according to NYHA classification.

Remodeling after myocardial infarction

Although difficult to quantify, the LV remodeling is a major factor, contributing to the development of infarct- related heart failure and death. It affects a substantial proportion of MI patients (38–40). However, among the post-MI patients, there is considerable heterogeneity considering responses to the LV remodeling (41). The infarction size seems to be the major determinant for unfavourable late remodeling (42). Therefore, it appears that the most severely affected patients with large infarctions and severe LV impairment could, theoretically, benefit from cellular therapy the most. Indeed, in the large REPAIR-AMI study, patients with the most severely impaired LV function showed the greatest improvement in LVEF following BMNCs infusion (33). The long-term left ventricular response to injury in patients with large necroses may differ from that in patients with small infarctions, as well as in patients with different MI locations and times to reperfusion. Differences in patient populations could be the reason for disparities in many of the reported study results. So far, in most of the studies the study populations consisted predominantly of patients with relatively mild LV impairments at baseline. Our study comprised a very homogenous group of patients with large first anterior MI, late reperfusion and significant LV impairment with LVEF which was considerably reduced compared to the previously published trials. Contrary to other studies, there were no significant differences in the course of the LV volume and functional changes by Month 4 between the actively treated patient group and the control group, however the long-term course was more favourable in the treated group. Early improvement in the LV function in both groups may reflect spontaneous healing and recovery, which occurs in more than 50 % of post-MI patients in the “reperfusion era” (43). However, the late functional improvement is suggestive of a long-term favourable effect of the BMNCs implantation on the LV remodeling, which is known to be a longstanding process (44). The mechanisms, through which the BMNCs transfer could enhance LV recovery and prevent or even reverse its remodeling, are poorly understood. Primary myocardial regeneration of new contractile tissue does not seem to be a likely mechanism, considering the small amount of cells (1–5 %) retained within the myocardium for 24–48 hours after their implantation (45). Although it has been advocated that adult peripheral CD34+ cells can transdifferentiate into cardiomyocytes, endothelial and smooth muscle cells in vivo (46), this potential was not confirmed by other studies (47, 48). Other mechanisms, possibly mediated by paracrine action of the implanted BMNCs, were proposed (49). These could include increased angiogenesis leading to improved blood supply to the ischemic region (50) or inhibition of cardiomyocyte apoptosis in the infarction border zone (5). Our data suggest that the effects of BMNCs implantation on LV remodeling could extend far beyond the immediate post- infarction period, possibly through improved healing and scar formation, as well through effects on contractile and vascular elements alone.

Study limitations

The present study has several limitations. Because no functional effects were demonstrated at Month 4 and because some early fatal cardiac complications were recorded in the actively treated patients, the study had been stopped early by the steering committee before the target number of patients was reached. Therefore, the number of patients in our study is too small to be able to draw definitive conclusions on the BMNCs therapy long-term effects. Although no causal relationship between the early complications in the actively treated patients and the BMNCs harvest was demonstrated, inherent risks of this procedure in hemodynamically fragile, post-MI patients can not be completely ruled out.

The control group patients were not administered sham BMNCs infusions and sole effects of intermittent infarct- related artery occlusions on LV remodeling can not be completely excluded. Finally, neither patients, nor their physicians were blinded to the treatment modality, therefore the clinical status assessments with respect to cell implantation were unreliable.

Conclusion

In our randomized study, no additional benefits of the BMNCs intracoronary infusion were observed when compared to the current reperfusion strategy in patients with large acute anterior myocardial infarction and late presentation, during the short- term follow up period. However, the long-term follow-up study of the BMNCs transplantation was associated with significant improvements in global LVEF. Although there were no differences in the early LV volume and function changes between the treatment group and the spontaneous healing control group, the long- term follow up outcomes suggest possible long-term protective effects against unfavourable LV remodeling. Although current data on the method’s clinical efficacy are ambiguous and information on its mechanisms of action is controversial, the evidence of potential short-term and long-term positive effects on LV remodeling and repair is growing. The persisting uncertainty concerning clinical relevance of the stem cells implantation after MIs can only
be resolved by large randomised clinical trials with hard clinical endpoints, which are currently conducted. Further progress in our understanding of the basic mechanisms of action, as well as further refinement in the cell selection and modes of application are clearly needed to enhance efficacy of the repair process following cellular therapy, before the method can be recommended for widespread clinical use.

References


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