Intracoronary Injection of Autologous Bone Marrow-Derived Mononuclear Cells in Patients With Large Anterior Acute Myocardial Infarction
A Prematurely Terminated Randomized Study

To the Editor: One-third of patients with ST-segment elevation myocardial infarction, usually those presenting late, show ongoing left ventricular (LV) remodeling and poor clinical outcome despite primary percutaneous coronary intervention (PCI) (1). Cardiac transfer of bone marrow-derived stem cells has been investigated as an adjunctive therapy to promote the repair of infarcted myocardium (2–5). Therefore, we designed a randomized study to test the safety and efficacy of intracoronary injection of autologous bone marrow–derived mononuclear cells (BMNCs) in patients with large acute anterior myocardial infarction and late presentation who were treated with successful primary PCI.

The study population consisted of 27 consecutive patients (age 59 ± 12 years; 81% males) with the first ST-segment elevation acute anterior myocardial infarction due to occlusion of the proximal left anterior descending artery (LAD) who had undergone successful primary stented PCI. Patients were eligible if they had primary PCI from 4 to 24 h after symptoms onset and showed a reduced LV ejection fraction ≤50% with at least 3 akinetic segments in the LAD territory. The study protocol was approved by the Medical Ethical Committees from all involved institutions, and informed consent was obtained from all patients.

Eligible patients were randomly assigned in a 2:1 ratio either to intracoronary BMNCs injection (n = 17) or standard medical therapy (n = 10). In the BMNCs group, aspiration of BMNCs was performed 4 to 11 days after PCI. After isolation, mononuclear BMNCs concentrate was infused in the LAD using a stop-flow technique through an over-the-wire balloon catheter (2). At baseline and 4-month follow-up, LV ejection fraction and volumes were assessed by echocardiography with the biplane Simpson methods, infarct size with single-photon emission computed tomography combining perfusion by technetium-99m sestamibi and glucose uptake by F-18-fluorodeoxyglucose. Coronary angiography was repeated at 4 months. All statistical analyses were conducted according to the intention-to-treat principle. Two-sided paired and unpaired Student t test or Fisher exact test was used as appropriate. For all tests, p < 0.05 was considered significant.

Baseline characteristics, including infarct size (maximum creatine kinase 2,995 ± 1,975 U/l vs. 2,751 ± 789 U/l, p = ns), degree of LV dysfunction (ejection fraction 38 ± 7% vs. 39 ± 4%, p = NS) and proportion of patients with Thrombolysis In Myocardial Infarction flow grade 3 after PCI (77% vs. 80%, p = NS) were comparable between groups. The median time from pain onset to PCI was >5 h (interquartile range [IQR] 5 to 11) in both groups (p = NS). The median time from PCI to BMNCs intracoronary injection was 9 days (range 4 to 11 days). On average, 171 ± 48 ml of bone marrow blood was harvested and processed to a final volume of 27 ± 7 ml. The median number of injected BMNCs and CD34+ cells was 26.4 × 10^6 (IQR 19.6 × 10^6 to 33.0 × 10^6) and 1.3 × 10^6 (IQR 1.1 × 10^6 to 1.4 × 10^6), respectively. The viability of BMNCs ranged from 94% to 99%. Intracoronary transfer of BMNCs was successful in all patients, and no serious periprocedural complications or increase in cardiac markers were observed.

At 4-month follow-up (Table 1), infarct size decreased, and LV ejection fraction improved to a similar extent in both groups whereas LV volumes did not change significantly. In the BMNCs group, insignificantly more dysfunctional segments showed improvement in contractile function as compared with the control group.

Regarding the safety, 2 patients developed serious complications during or after bone marrow harvest. One patient had a ventricular septal rupture before the injection of BMNCs, underwent emergency surgery, and died 3 months later as the result of severe heart failure. The other patient suffered a stent thrombosis with reinfarction immediately after we harvested the BMNCs. He had a complicated PCI followed by coronary artery bypass grafting and died 2 weeks later from sepsis and acute respiratory distress syndrome. Another patient had diagnosed biliary carcinoma 6 weeks after BMNCs’ transfer and died 2 months later. One BMNC patient suffered from reinfarction due to LAD occlusion distally to the implanted stent 9 months after randomization.

One patient in each group was hospitalized for worsening heart failure. The rate of revascularization was similar in both groups (24% in the BMNCs group and 40% in the control group; p = NS). At 12-month follow-up, LV ejection fraction (46 ± 7% vs. 49 ± 13%; p = NS) improved to a similar extent. No patient developed malignant arrhythmias. The original intention was to enroll a total of 40 patients in the BMNCs group and 20 patients in the Control group. After enrollment of the initial 27 patients, the trial was terminated prematurely because of the unexpected occurrence of serious complications in the BMNCs group and no incremental functional effects of BMNCs as compared with control patients.

This randomized study showed that, in patients with large acute anterior myocardial infarction and late presentation, intracoronary infusion of BMNCs in the infarct-related coronary artery at a median of 9 days after primary PCI does neither increase recovery of LV ejection fraction nor reduce LV volumes and infarct size at 4 months, as compared with control subjects. Four randomized trials (2–5) have been conducted so far to investigate the functional

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Nevertheless, corroborating data from previous trials (3,5), did ejection fraction 6.7% to 11.3% lower than in all previous trials. In the present study, we enrolled a homogenous population of fraction in the BMNCs group as compared with control patients. (4) reported enhanced and sustained recovery of LV ejection effects of BMNCs intracoronary injection in patients with smaller.

The 4-month functional follow-up data are reported in 14 patients in the BMNCs group who survived the first 4 months after randomization. †p 0.01 baseline versus follow-up. BMNC = bone marrow-derived mononuclear cell; LAD = left anterior descending; LV = left ventricular; NS = not significant; SPECT = single-photon emission computed tomography.

effects of BMNCs intracoronary injection in patients with smaller acute myocardial infarction with controversial results. Only 1 trial (4) reported enhanced and sustained recovery of LV ejection fraction in the BMNCs group as compared with control patients. In the present study, we enrolled a homogenous population of patients with extensive anterior myocardial infarction with an ejection fraction 6.7% to 11.3% lower than in all previous trials. Nevertheless, corroborating data from previous trials (3,5), did not observe any improvement in ejection fraction by BMNCs over primary PCI alone. Low regenerative potential (6) and low engraftment after intracoronary injection (7) may be the major explanations for lack of functional effects of BMNCs.

The present study has several limitations. The number of enrolled patients was small, and the study was terminated prematurely. Hence, the potential treatment effect could be missed. Yet, inclusion of more patients would have not likely to change the results. In contrast to previous studies, we included patients with poor LV function, late revascularization, and late BMNCs injections. It may be possible that this subset of patients does not benefit from the transplantation of BMNCs. Hence, our results are not necessarily in contradiction with positive results of larger trials (4). It should be pointed out that adverse events observed in the study do not seem to be directly related to the BMNCs procedure. No complications were observed during the injection of BMNCs. Given the laborious nature of BMNC harvest and intracoronary transfer, small, if any, functional effects, and lack of prognostic data, the routine use of BMNCs after acute myocardial infarction cannot be recommended at the present time.

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Table 1: LV Systolic Global and Regional Function, LV Volumes, and Infarct Size at Baseline and 4-Month Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>BMNCs Group (n = 14)*</th>
<th>Control Group (n = 10)</th>
<th>p Value Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>Value</td>
<td>Change From Baseline</td>
<td>Value</td>
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<tr>
<td>Baseline</td>
<td>163 ± 30</td>
<td></td>
<td>162 ± 30</td>
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<tr>
<td>4 months</td>
<td>172 ± 34</td>
<td>↑ 5.5%</td>
<td>174 ± 29</td>
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<tr>
<td>LV end-systolic volume (ml)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>98 ± 25</td>
<td></td>
<td>98 ± 23</td>
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<tr>
<td>4 months</td>
<td>95 ± 28</td>
<td>↓ 3.1%</td>
<td>96 ± 28</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>39 ± 6</td>
<td></td>
<td>39 ± 4</td>
</tr>
<tr>
<td>4 months</td>
<td>45 ± 9†</td>
<td>↑ 15.4%</td>
<td>47 ± 7†</td>
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<tr>
<td>Akinetic and severely hypokinetic segments in the LAD perfusion territory</td>
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<tr>
<td>Baseline</td>
<td>5.9 ± 1.6</td>
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<td>5.8 ± 1.8</td>
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<tr>
<td>4 months</td>
<td>3.5 ± 2.6‡</td>
<td>↓ 40.7%</td>
<td>3.8 ± 2.4‡</td>
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<tr>
<td>Infarct size at SPECT (%)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>41.4 ± 18.3</td>
<td></td>
<td>47.5 ± 20.8</td>
</tr>
<tr>
<td>Follow-up</td>
<td>30.5 ± 16.1‡</td>
<td>↓ 26.3%</td>
<td>35.3 ± 17.2‡</td>
</tr>
</tbody>
</table>


REFERENCES


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