Peripheral blood stem cells transplantation in patients with heart failure after myocardial infarction: their efficiency and safety

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Objective To compare the efficiency and safety of intracoronary transplantation of peripheral blood stem cells (PBSC) between elderly and younger patients with heart failure after myocardial infarction (MI).

Methods Twenty-five patients with heart failure after MI were divided into aged group (≥60 years, n=13) and non-aged group (<60 years, n=12) to receive intracoronary PBSC transplantation (PBSCT) following bone marrow cells mobilized by granulocyte colony-stimulating factor (G-CSF). Clinical data including coronary lesion characteristic, left ventricular shape, infarct region area and cardiac function, as well as adverse side effects between the two groups were compared. Left ventricular function was evaluated before and 6 months after the treatment by single photon emission computed tomography (SPECT).

Results At 6 months, the left ventricular ejection fraction (LVEF) and 6 minute walk test (6MWT) distance increased, while the left ventricular diastolic diameter (LVDd) decreased significantly in both groups. There were no significant difference between the two groups in absolute change in the cardiac function parameters.

Conclusions The present study demonstrated that autologous intracoronary PBSCT might be safe and feasible for both old and younger patients with heart failure after MI and left ventricular function is significantly improved.

Key Words G-CSF; stem cells; transplantation; myocardial infarction; heart failure

Introduction

Acute myocardial infarction (AMI) and the subsequent heart failure are major causes of mortality and morbidity around the world, especially in elderly patients. Current treatment modalities for AMI such as medical thrombolytic therapy, antiplatelet and anti-coagulation medications, percutaneous coronary intervention (PCI) and surgical intervention have led to improved prognosis for AMI patients, but their effects are not very satisfactory. One of the recent progresses in the treatment of AMI is autologous stem cell transplantation, in which hemopoietic stem cells (HSCs) from bone marrow (BM) are mobilized by granulocyte colony-stimulating factor (G-CSF) into peripheral blood (PB), collected and infused into the infarct-related artery (IRA).1-4 Our research aimed to evaluate the safety and efficiency of intracoronary transplantation of autologous peripheral blood stem cells (APBSCs) mobilized by G-CSF in the treatment of patients with heart failure after AMI, and compared the results in old and younger patients.
The Institutional Review Board of our hospital approved the study protocol.

**Stem cell mobilization, characterization, and intracoronary infusion**

PBSC mobilization, separation, purification and collection

Patients received subcutaneous injection of G-CSF (Geneleukim) with the dose of 5 mg/kg/d, twice a day for 5 days. The leukocyte count was monitored. At day 6, PBSCs were separated and collected with Baxter CS 3000 blood cell separator. Before collection of PBSCs, patients received intravenous injection of dexamethasone with the dose of 10mg and hemoglobin concentration was checked. The infusion cell doses were about 15ml of cell suspension per patient, with PBSC of 1×10^7 per milliliter and CD34^+ cell population of 0.3-0.8%. The composition of mobilized cells were evaluated by flow cytometry.

Intracoronary infusion of PBSCs

PBSCs were infused into the infarcted-related coronary via over-the-wire Foley’s balloon catheter, with 5 ml of cell suspension each at the proximal, middle and distal end of the target vessel. In none but the first patient, coronary blood flow was blocked by intracoronary balloon inflation.

**Safety evaluation and follow-up of patients**

To study the safety of G-CSF–based stem cell therapy, the development of major adverse cardiac events (MACE); clinical status including G-CSF–related pain, dyspnea, and chest pain; hemoglobin concentration, biochemical tests including creatine kinase (CK)-MB, troponin, and blood cell counts, were evaluated before and after cell transplantation during admission. All patients were follow-up for 6 months and electrocardiogram, echocardiography and ambulatory electrocardiogram were monitored during the follow-up.

**Assessment of cardiac function and myocardial perfusion**

Cardiac function was assessed before and at 6 months after transplantation, using echocardiography and SPECT imaging. Left ventricular ejection fraction (LVEF) and LV volumes were calculated. Six minute walk test was also performed in all patients of both groups.

To determine myocardial perfusion, myocardial SPECT was performed in 6 patients in the aged group, and 7 patients in non-aged group, before and 6 months after cell transplantation. SPECT was reconstructed with a Butterworth cut-off frequency of 0.45, with an order of 5 and the reconstructed data were created along three oblique axis (short axis, vertical long axis and horizontal long axis) planes by setting the axes of the heart. Quantitative analysis was performed using Cedars quantitative perfusion SPECT (QPS). Perfusion defects were calculated using a scintigraphic bull’s eye technique.

**Statistical analysis**

Continuous variables were presented as mean ± SD. Differences in variables of the same group were compared with paired t test. Differences in variables of the 2 groups were compared with Student’s t test. A value of \( P < 0.05 \) was considered statistically significant. Statistical analysis was performed with SPSS (version 10.0, SPSS Inc).

**Results**

**Baseline clinical characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aged group(n=13)</th>
<th>Non-aged group(n=12)</th>
</tr>
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<tbody>
<tr>
<td>Age(yr)</td>
<td>66.85±4.58</td>
<td>52.08±5.07</td>
</tr>
<tr>
<td>Female</td>
<td>2(15.4)</td>
<td>1(8.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7(53.8)</td>
<td>7(58.3)</td>
</tr>
<tr>
<td>NYHA class ≥II</td>
<td>13(100)</td>
<td>12(100)</td>
</tr>
<tr>
<td>Plasma creatinine ≥170 μmol/L</td>
<td>2(15.4)</td>
<td>1(8.3)</td>
</tr>
<tr>
<td>Severe calcification of CA</td>
<td>8(61.5)</td>
<td>5(41.7)</td>
</tr>
<tr>
<td>COPD</td>
<td>3(23.1)</td>
<td>1(8.3)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9(69.2)</td>
<td>7(58.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>7(53.8)</td>
<td>8(66.7)</td>
</tr>
<tr>
<td>Diseased vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CA</td>
<td>7(53.8)</td>
<td>8(77.8)</td>
</tr>
<tr>
<td>2 CA</td>
<td>3(23.1)</td>
<td>3(25)</td>
</tr>
<tr>
<td>3 CA</td>
<td>3(23.1)</td>
<td>1(8.3)</td>
</tr>
<tr>
<td>Complete revascularization</td>
<td>10(76.9)</td>
<td>10(83.3)</td>
</tr>
</tbody>
</table>

COPD=chronic obstructive pulmonary disease; CA=coronary artery; NYHA=New York Association;
As shown in Table 1, except for the mean age, there were no significant differences between the 2 groups in regard to gender, history, cardiac function at admission, coronary artery lesions. PCI was successful in all patients of both groups.

Clinical course and safety evaluation

At 6 months, there were no deaths or MIs in both groups. One patient in aged group was rehospitalized because of heart failure and pulmonary infection. In aged group, NYHA class was improved by 1 grade in 6 patients, 2 in 3 patients and 3 in 3 patients. In non-aged group, NYHA class was improved by 1 grade in 6 patients, 2 in 3 patients and 3 in 3 patients. Six minute walk distance increased from 220.46 ± 22.32 meters to 280.85 ± 44.39 meters in aged group, whereas from 215.17 ± 20.72 meters to 288.67 ± 47.16 meters in non-aged. There was no significant difference in the absolute increase between the 2 groups.

G-CSF was well tolerated, with one patient presenting transient bone discomfort and one patient fatigue after G-CSF injection. However, during PBSC collection, one of the patient had diaphoresis and, hypotension. ECG showed accelerated ventricular independent rhythm. PBSCs intracorony infusion was not performed and he recovered with medical management. Another patient had acute pulmonary edema, severe bradycardia and Adams-Stokes syndrome when Over-The-Wire balloon was being inflated and the PBSCs were being infused. He also recovered after stopping PBSC infusion and medical treatment. No G-CSF–related symptoms such as bone pain, dyspnea, and chest pain were observed in all other patients. There were no abnormal finding regarding to hemoglobin concentration, biochemical tests including CK-MB, troponin, and blood cell counts during the follow-up period.

Cardiac function and myocardial perfusion

LVEF, as assessed by echocardiography, improved significantly at 6 months in both groups, while left ventricular end-diastolic diameter (LVEDd) decreased. As shown in Table 2, there were no differences of intra-group changes of LVEF and LVEDd before and 6 months after PBSCs transplantation.

SPECT was performed in 13 patients (6 in the aged group and 7 in the non-aged group) to evaluate myocardial perfusion. As shown in Fig 1, the percentage of perfusion defect size decreased in patients of both groups.

Discussion

G-CSF and cell therapy for AMI

Treatment of acute myocardial infarction and subsequent heart failure remains a great challenge despite tre-

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Table 2 Cardiac function and 6MWT distance in the 2 groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Aged group (n=13)</th>
<th>Non-aged group (n=12)</th>
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<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>At 6 months</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>61.92 ± 7.06</td>
<td>56.30 ± 5.39</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>41.85 ± 4.54</td>
<td>45.31 ± 3.28</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>220.46 ± 22.32</td>
<td>280.85 ± 44.39</td>
</tr>
<tr>
<td></td>
<td>60.17 ± 6.62</td>
<td>55.17 ± 6.74</td>
</tr>
<tr>
<td></td>
<td>38.33 ± 4.32</td>
<td>43.83 ± 5.42</td>
</tr>
<tr>
<td></td>
<td>215.17 ± 20.72</td>
<td>288.67 ± 47.16</td>
</tr>
</tbody>
</table>

LVEDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; 6MWT = 6 minute walk test.

*P < 0.05, compared with before transplantation.

Fig 1 Myocardial perfusion before and 6 months after intracoronary PBSCT transplantation.
mendous progress in prompt reperfusion therapy during the past decades. Cell therapy with bone marrow derived stem cells to regenerate damaged myocardium in patients seems promising.\(^5\)\(^-\)\(^7\) Two different stem cell treatment modalities have been evaluated in clinical trials. Patients were either treated with intracoronary or direct intramyocardial-delivered bone marrow stem cell solutions, or treated with prolonged pharmacological stem cell mobilization from the bone marrow into the peripheral circulation. G-CSF has been used in several clinical trials in patients with AMI and in patients with chronic myocardial ischemia. However, results are not consistent.\(^8\)\(^-\)\(^10\)

Several studies have investigated the effects of intracoronary infusion of G-CSF mobilized PBSCs on left ventricular function and reported favorable results.\(^1\)\(^-\)\(^4\) G-CSF–based stem cell therapy has been proposed as a practical and noninvasive alternative to stem cell therapy using bone marrow stem cells.\(^1\)\(^-\)\(^4\) Previous studies also showed that in patients with MI, intracoronary infusion of PBSCs improved cardiac function and exercise capacity, whereas the administration of G-CSF alone did not.\(^11\) Our study showed that G-CSF is safe and potentially able to ameliorate left ventricular function and perfusion after AMI. We found that G-CSF was associated with a considerable improvement in left ventricular function and myocardial perfusion at follow-up. Our result was in consistent with these reports and further demonstrated the efficacy of intracoronary infusion of G-CSF mobilized PBSCs as a treatment modality for patients with AMI.

**Aging and stem cell therapy in AMI**

Advanced age is a major risk factor for ventricular dysfunction and reduction of cardiac reserve. Elderly patients with AMI are at much greater risk to develop heart failure than younger patients. Two CHD deaths out of three occurred in patients aged 65 years and over.\(^12\) So finding novel approaches to prevent and attenuate heart dysfunction associated with myocardial infarction is a major therapeutic challenge. A recent meta-analysis, which included five primary randomized, controlled trials across 326 patients of G-CSF as adjunctive therapy to the standard therapy versus the standard therapy in patients with recent MI, showed that the addition of G-CSF was associated with a lower risk of target-vessel restenosis and cumulative cardiovascular events, a significant improvement of left ventricular ejection fraction in patients with mean age<55 years but not in the elderly (mean age \(\geq\)55 years).\(^13\) In rat model of MI, Lehrke and colleagues\(^14\) found that, although the G-CSF/SCF cocktail reduced cardiac myocyte apoptosis in old as well as in young hearts, the degree of reduction was substantially less with age and the rate of cardiomyocyte apoptosis in old animals remained high despite cytokine treatment.

However, in contrast to most of other studies, our results showed that LV function was improved not only in younger patients, but in elderly patients over 60 years as well. There were no differences regarding LV function, 6 minute walk distance and myocardial perfusion improvement between the aged and non-aged patients. In another study, also on Chinese patients, Li and colleagues\(^4\) reported significant improvement of left ventricular function after autologous PBSCs transplantation by intracoronary infusion compared with placebo. The average age of their patients was 60 ± 10 years. Currently we can not provide ready explanation for the different results between ours and others. But our study suggested the importance of evaluating efficacy of treatments for AMI in different population.

**Safety issue**

The safety of autologous stem cells transplantation has been paid growing attention in recent years. In one study, Kang et al\(^15\) found in-stent restenosis in five of seven patients treated with G-CSF for 5 days, followed by bare metal stent implantation and by intracoronary BMC infusion; notably, they found a correlation between late loss and improvement in the LVEF at follow-up. In addition, in a non-randomized study in 38 patients, Mansour et al\(^16\) found that the infusion of CD133\(^-\)-enriched BMC was associated with greater in-stent proliferation and larger luminal loss in non-stented distal segments of the infarct-related artery, which resulted in a significant decrease in coronary flow reserve.\(^16\) However, in a more recent study also by Kang and colleagues found an improvement in the LVEF in the absence of a higher rate of in-stent restenosis in post-AMI patients successfully revascularized by drug-eluting stent (DES) implantation, who received G-CSF, followed by intracoronary BMC infusion. It has been suggested that the anti-inflammatory effect of DES be probably sufficient to counterbalance the potential pro-inflammatory action of G-CSF.\(^17\)

In the present study of both aged and younger patients with AMI, no severe adverse reaction to G-CSF was observed during the mobilization phase. One patient developed hypotension and cardiac arrhythmia during the intracoronary transplantation procedure, which might be caused by other factors rather than cell transplantation itself. Except for one patient, who was readmitted to hospital for heart failure, presumably triggered by pneumonia, no major adverse cardiac events, including reinfarction and cardiac death, were found during the 6 month’s follow up. Our results were in consistent with observations by other researchers.

In conclusion, our study showed intracoronary infusion of G-CSF mobilized PBSCs as an adjunctive therapy in AMI patient who had successfully performed PCI, was safe and feasible. This treatment was associated with improvement of LV function and myocardial perfusion not only in younger patients, but also in elderly patients. However, our study is a small, uncontrolled study, and the results should
be confirmed by further large, double-blind, randomized, controlled trials for the use of autologous bone marrow cells in the treatment of AMI.18

References


