Isolated Coronary Artery Bypass Graft Combined With Bone Marrow Mononuclear Cells Delivered Through a Graft Vessel for Patients With Previous Myocardial Infarction and Chronic Heart Failure

A Single-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Objectives

This study aimed at examining the efficacy of bone marrow mononuclear cell (BMMNC) delivery through graft vessel for patients with a previous myocardial infarction (MI) and chronic heart failure during coronary artery bypass graft (CABG).

Background

Little evidence exists supporting the practice of BMMNC delivery through graft vessel for patients with a previous MI and chronic heart failure during CABG.

Methods

From November 2006 to June 2009, a randomized, placebo-controlled trial was conducted to test the efficacy and safety of CABG for multivessel coronary artery disease combined with autologous BMMNCs in patients with congestive heart failure due to severe ischemic cardiomyopathy. Sixty-five patients were recruited, and 60 patients remained in the final trial and were randomized to a CABG + BMMNC group (n = 31) and a placebo-control group (i.e., CABG-only group, n = 29). All patients discharged received a 6-month follow-up. Changes in left ventricular ejection fraction from baseline to 6-month follow-up, as examined by magnetic resonance imaging, were of primary interest.

Results

The overall baseline age was 59.5 ± 9.2 years, and 6.7% were women. After a 6-month follow-up, compared with the placebo-control group, the CABG + BMMNC group had significant changes in left ventricular ejection fraction (p = 0.029), left ventricular end-systolic volume index (p = 0.017), and wall motion index score (p = 0.011). Also, the changes in the distance on the 6-min walking test as well as B-type natriuretic peptide were significantly greater in the CABG + BMMNC group than in the control group.

Conclusions

In summary, patients with a previous MI and chronic heart failure could potentially benefit from isolated CABG (i.e., those who received CABG only) combined with BMMNCs delivered through a graft vessel. (Stem Cell Therapy to Improve Myocardial Function in Patients Undergoing Coronary Artery Bypass Grafting [CABG]; NCT00395811) (J Am Coll Cardiol 2011;57:2409–15) © 2011 by the American College of Cardiology Foundation
Abbreviations and Acronyms

- **BMMNC** = bone marrow mononuclear cell
- **BNP** = B-type natriuretic peptide
- **CABG** = coronary artery bypass graft
- **LV** = left ventricular
- **LVEDV** = left ventricular end-diastolic volume
- **LVEF** = left ventricular ejection fraction
- **LVESVI** = left ventricular end-systolic volume index
- **MI** = myocardial infarction
- **MRI** = magnetic resonance imaging
- **6MWT** = 6-min walking test
- **PMI** = previous myocardial infarction
- **SPECT** = single-photon emission computed tomography

There is well-established evidence of the benefit of revascularization for reviving stunned or hibernating myocardium in patients with ischemic heart disease (1). However, the ventricular remodeling process is generally irreversible, especially in patients with end-stage ischemic cardiomyopathy (1). Cell transplantation, as represented by bone marrow–derived cell transplantation, gives rise to a new therapeutic method for patients with ischemic cardiomyopathy (2). A number of randomized trials have shown that in patients with acute myocardial infarction (MI), stem cell transplantation through various ways will improve the left ventricular ejection fraction (LVEF) and reverse, to a certain extent, ventricular remodeling (3–5). Despite the promising results, the evidence regarding the therapeutic effect of cell transplantation in patients with a previous MI (PMI) and heart failure is still lacking (6,7). Our previous observational studies have shown that a coronary artery bypass graft (CABG) combined with autologous bone marrow mononuclear cells (BMMNCs) appeared to be feasible and safe for this group of patients (8). To establish further the efficacy and safety of CABG + BMMNCs in patients with PMI and heart failure, we conducted a randomized trial involving 60 patients recruited in a single center.

**Methods**

This study was a randomized, placebo-controlled trial of the efficacy and safety of a CABG combined with autologous BMMNCs in patients presenting with congestive heart failure due to severe ischemic cardiomyopathy.

**Patient population.** The recruitment took place between November 2006 and June 2009. Patients of ages 18 to 75 years with congestive heart failure and suitable for elective CABG surgery were considered for the study. Patients were eligible if they had met all the following conditions: 1) at least 3 months since the last MI; 2) planned CABG for triple-vessel disease and according to American Heart Association guidelines (Indications for CABG in Poor LV Function) (9); 3) no evidence of surviving myocardium in the infarct area, as shown by single-photon emission computed tomography (SPECT) and left ventricular angiography; 4) LVEF <30% on magnetic resonance imaging; and 5) without left ventricular (LV) aneurysm or valvular diseases requiring surgical intervention. Patients were not eligible if they had any one of the following conditions: 1) mitral regurgitation, LV aneurysm, or intraventricular thrombus requiring concurrent surgery by transesophageal echocardiography during operation; 2) contraindications to cardiac magnetic resonance imaging (MRI); 3) significant ventricular arrhythmias (sustained ventricular tachycardia) or atrial fibrillation; 4) primary hematologic diseases; 5) history of neoplasia or malignancy potentially influencing the patient’s survival; 6) unexplained abnormality at laboratory baseline value; 7) history of other severe chronic diseases; and 8) unwillingness to participate. All participants gave written informed consent at enrollment and received the same treatment and rehabilitation regimens as the standard CABG protocol.

**Procedures.** Patients were randomly assigned to the stem cell group or placebo-control group in a 1:1 ratio. In the current study, the placebo-control group refers to the CABG-alone group. The random table was generated by the SAS software version 9.13 (SAS Institute, Cary, North Carolina). After randomization, the study processes were blinded to the patients, participating surgeons, coordinators, and investigators who were responsible for patient assessment were blinded to the study processes. The study was approved by the ethics committee of Fuwai Hospital, Peking Union Medical College. The study protocol is shown in Figure 1.

Baseline data were collected pre-operatively, and outcomes such as all-cause death, MI, revascularization, and congestive heart failure were documented post-operatively. At 6 months after surgery, all patients underwent cardiac MRI, SPECT, and echocardiography assessment as well as a 6-min walking test (6MWT), and BNP value. The 24-h Holter electrocar-
Diagram was performed to monitor the occurrence of arrhythmias for all patients during all the trial sessions.

**Preparation and transplantation of BMMNCs.** On the day of the CABG procedure, BMMNCs were harvested from each patient in the operating room and processed in the Key Laboratory for Cardiovascular Regenerative Medicine, the Ministry of Health. After anesthesia but before CABG, 60 ml of bone marrow was aspirated from the patient’s iliac crest by an experienced hematologist and diluted with normal saline solution. The mononuclear cells were isolated using Ficoll (Amersham Biosciences, Piscataway, New Jersey) density gradient centrifugation according to good manufacturing practice regulations, and resuspended in 10 ml of saline solution. The cell suspension was filtered by a 70-μm cell strainer (Gibco, Grand Island, New York) before transplantation. The cells were counted under a light microscope, and the viability was assessed by trypan blue dye. The final suspension of BMMNCs contained $10^7$/ml mononuclear cells. The placebo solution was a mixture of 8 ml of saline solution and 2 ml of the patient’s own serum. After randomization, a syringe containing either bone marrow cell suspension or placebo solution was brought to the operating room.

All surgeries were performed by 2 senior surgeons, with the same anesthetists and perfusionists. Standard techniques were adopted by cardiopulmonary bypass, using cold antegrade cardioplegia, and moderate systemic hypothermia (28°C to 32°C). A left internal mammary artery graft was anastomosed to the left anterior descending artery, and saphenous vein was used for other target vessels. The blinded cell or placebo solution was injected via the saphenous vein bypass graft after distal anastomosis of the right coronary artery and left circumflex coronary artery. Each saphenous vein bypass graft area received 3 ml of solution, and 4 ml of solution was injected through distal left anterior descending artery anastomosis right before completion of distal left anterior descending artery bypass graft (Fig. 2).

**Outcome measures.** The primary endpoint for assessment of the efficacy was the changes in the LVEF from baseline to 6-month follow-up, assessed using MRI. Secondary efficacy endpoints were LV end-diastolic volume index by MRI, left ventricular end-systolic volume index (LVESVI) by MRI, wall motion index score by 3-dimensional echocardiography, perfusion score by SPECT, 6MWT, and BNP value.

During the current study, an independent data safety monitoring board met on a regular basis to review the efficacy and safety of the data, which included: 1) major cardiac adverse events, defined as the composite of all-cause death, resuscitated sudden death, MI, and congestive heart failure; and 2) arrhythmias as detected by 24-h Holter monitoring, with main categories including sustained ventricular fibrillation or polymorphic ventricular tachycardia, sustained monomorphic ventricular tachycardia at a rate >120 beats/min, wide-complex tachycardia of unclear type, sustained atrial fibrillation or flutter, bradyarrhythmia and
shock delivered by an implantable cardioverter-defibrillator, bradycardia, rhythmia pacing, or antitachycardia pacing.

**Cardiac MRI.** Cardiac MRI was performed using a 1.5-T scanner (Siemens Medical, Erlangen, Germany) with a surface body coil, electrocardiography gating, and respiratory triggering. Sequence parameters were as follows: balanced fast field echo gradient echo sequence with dynamic sequences in transversal plane; long-axis, short-axis, and 4-chamber views; and 3-dimensional T1-weighted fast field echo gradient echo sequence with multishot and TFE prepulse with variable delay between 200 and 300 ms after intravenous contrast injection of Magnevist (Bayer Schering Pharma, Morristown, New Jersey). Global parameters assessed include LVEF, LVEDV index (LVEDV index = LVEDV / body surface area), and LVESVI (LVESVI = LVESV / body surface area). Endocardial and epicardial borders were traced in all end-diastolic and end-systolic short axis and long axis slices to determine LVEDV and LVESV for calculation of global LVEF, with ejection fraction = (LVEDV – LVESV)/LVEDV) × 100%. Two experienced observers blinded to all clinical data analyzed the images.

All MRI was quantitatively analyzed by commercial software provided by Siemens (Syngo VD10B, Syngo VX49B, Argus VA60C).

**Echocardiography.** Regional myocardial contractility was measured by real-time transthoracic 3-dimensional echocardiography using a Philips IE33 ultrasound system (Philips Medical Systems, Irvine, California). Regional LV wall motion analysis was performed as described by the Committee on Standards of the American Society of Echocardiography, by dividing the left ventricle into 16 segments and scoring wall motion for each segment as 1 (normal), 2 (hypokinesis), 3 (akinesis), or 4 (dyskinesis). The wall motion index score was calculated as the sum of the scores of the segments divided by the number of segments evaluated.

**Single-photon emission computed tomography.** Myocardial perfusion imaging was performed by gated SPECT (Siemens Medical) 90 min after technetium-99m sestamibi was intravenously injected. Myocardial 18F-fluorodeoxyglucose imaging was performed by SPECT with an ultra-high energy collimator. Myocardial perfusion was analyzed using Cedars-Sinai Quantitative Perfusion SPECT software (Cedars–Sinai, Los Angeles, California). To assess the improvement in myocardial perfusion and viability after intervention, relative segment of technetium-99m sestamibi and 18F-fluorodeoxyglucose uptake were calculated as a percentage of uptake of the segment with maximal uptake (normalization to the 100% perfusion maximum). The left ventricle was divided into 17 segments according to the American Heart Association/ American College of Cardiology recommendations, and image analysis was performed using semiquantitative analysis. The segmental tracer activity was categorized on a 4-point scale: 1 denoting tracer activity of >75%; 2 denoting tracer activity of 50% to 75%; 3 denoting tracer activity of 25% to 49%; and 4 denoting tracer activity of <25%. Perfusion defects on stress images were considered present when tracer activity was <75% of maximum. When significant fill-in (>10%) of perfusion defects was observed on the resting images, segments were classified as ischemic.

**Statistical analysis.** Sample size estimation was based on a clinically relevant increase in LVEF of at least 5%. A standard error of 2% was expected at each assessment of the LVEF (the standard error of the mean of 3 baseline studies estimated to 1%). Given these assumptions to detect a true

<table>
<thead>
<tr>
<th>Table 1 Baseline Characteristics</th>
<th>CABG + BMMNC Group (n = 31)</th>
<th>Placebo-Control Group (n = 29)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs</strong></td>
<td>56.61 ± 9.72</td>
<td>58.27 ± 8.86</td>
<td>0.501</td>
</tr>
<tr>
<td><strong>NYHA functional class</strong></td>
<td>3 (2, 3)</td>
<td>2 (2, 3)</td>
<td>0.469</td>
</tr>
<tr>
<td><strong>CCS class</strong></td>
<td>1 (2, 3)</td>
<td>2 (2, 3)</td>
<td>0.101</td>
</tr>
<tr>
<td><strong>No. of grafts</strong></td>
<td>4 (4.0, 4.5)</td>
<td>4 (4.0, 4.5)</td>
<td>0.537</td>
</tr>
<tr>
<td><strong>CPB time, min</strong></td>
<td>91 (79, 103)</td>
<td>89 (80, 116)</td>
<td>0.299</td>
</tr>
<tr>
<td><strong>Clamping time, min</strong></td>
<td>59 (47, 68)</td>
<td>53 (47, 73)</td>
<td>0.975</td>
</tr>
<tr>
<td><strong>Ventilation time, h</strong></td>
<td>16 (13.5, 19.5)</td>
<td>17 (15.20)</td>
<td>0.358</td>
</tr>
<tr>
<td><strong>ICU stay, days</strong></td>
<td>3 (4.0, 5.5)</td>
<td>3 (3, 4)</td>
<td>0.257</td>
</tr>
<tr>
<td><strong>MRI LVEDVI, ml/m²</strong></td>
<td>106.20 (90.10, 121.55)</td>
<td>93.33 (83.35, 111.13)</td>
<td>0.116</td>
</tr>
<tr>
<td><strong>MRI LVESVI, ml/m²</strong></td>
<td>80.13 (67.18, 101.89)</td>
<td>71.51 (62.61, 84.11)</td>
<td>0.140</td>
</tr>
<tr>
<td><strong>MRI LVEF</strong></td>
<td>22.78 (19.76, 27.46)</td>
<td>24.95 (20.72, 29.15)</td>
<td>0.287</td>
</tr>
<tr>
<td><strong>Echo segment movement score</strong></td>
<td>39 (36, 41)</td>
<td>38 (36, 40)</td>
<td>0.460</td>
</tr>
<tr>
<td><strong>Ratio of complete MI, %</strong></td>
<td>18.95 ± 3.92</td>
<td>24.60 ± 11.71</td>
<td>0.185</td>
</tr>
<tr>
<td><strong>Ratio of complete MI, %</strong></td>
<td>33.99 ± 12.40</td>
<td>28.88 ± 11.60</td>
<td>0.355</td>
</tr>
<tr>
<td><strong>6-min walking test</strong></td>
<td>466 (402, 495)</td>
<td>448 (383, 497)</td>
<td>0.272</td>
</tr>
<tr>
<td><strong>BNP</strong></td>
<td>1.329 (704, 1653)</td>
<td>862 (680, 1646)</td>
<td>0.439</td>
</tr>
</tbody>
</table>

Values are mean ± SD or median (quartile). BNP = B-type natriuretic peptide; BMMNC = bone marrow mononuclear cell; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; CPB = cardiopulmonary bypass; ICU = intensive care unit; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; MRI = magnetic resonance imaging; NYHA = New York Heart Association.
increase in the LVEF of 6% with an SD of 8% and a power of 80%, a sample size of 52 patients was required.

Continuous variables are presented as mean ± SD, unless otherwise specified. Categorical variables were compared between the 2 treatment groups using the chi-square test or Fisher exact test. Statistical comparisons between the initial and follow-up data were performed in a nonparametric, paired fashion using Wilcoxon signed-rank test. Nonparametric Mann-Whitney U tests and Kruskal-Wallis tests were used to compare continuous variables with categorical variables as well as to compare the results between treatment groups. All the statistical analyses were performed using SAS version 9.13 (SAS Institute).

Results

Baseline characteristics. From November 2006 to June 2009, 65 patients were evaluated for eligibility and 5 patients were excluded because they had to undergo concomitant mitral valve repair or ventricular aneurysmectomy. Of the 60 patients randomized (31 in the CABG + BMMNC group and 29 in the placebo-control group), there was a good balance between the 2 groups with respect to baseline characteristics (Table 1). Mean ± SD age was 59.5 ± 9.2 years, and 6.7% were women (n = 4). The heart function classification of the New York Heart Association averaged 2.5 ± 0.6, and 43 patients had a history of heart failure. Seven patients had a history of malignant arrhythmia (ventricular tachycardia or fibrillation) and were successfully converted electrically. The LVEF examined by MRI ranged from 13% to 29% and averaged 0.23 ± 0.6. The SPECT perfusion imaging showed a ratio of borderline MI of 22.06 ± 9.03% and a ratio of complete MI of 31.18 ± 11.93%.

The harvested BMMNCs. The number of harvested BMMNCs ranged from 1.08 to 70 × 10^7 with an average of 13.17 ± 10.66 × 10^7. The ratio of viable BMMNCs was >98%. The BMMNCs have proliferative potential in vitro. The primary cell formed a clone at approximately 10 days, and the time from primary passage to the first passage was 12 to 14 days. Microbiological examination showed no contamination of the culture.

Intraoperative and early post-operative outcomes. Of the 60 patients enrolled, the number of grafts was 4 ± 0.7 (range 3 to 5 grafts) and the cardiopulmonary bypass time was 90 ± 18 min (range 61 to 154 min). Nine patients were assisted by intra-aortic balloon pump because of postoperative pulmonary capillary wedge pressure >20 mm Hg, and all were weaned successfully from the intra-aortic balloon pump at 1 to 3 days after surgery and discharged. One patient received an LV assist device (BVS5000, Abiomed, Danvers, Massachusetts) and weaned 7 days later. The ventilation time was 22 ± 36 h (range 7 to 168 h) and the length of intensive care unit stay was 5 ± 1 days (range 1 to 36 days). Two patients had neurological com-

<table>
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<tr>
<th>Table 1 Change in MRI Indexes After Surgery (x ± s)</th>
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<tr>
<td>Pre-Operative</td>
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<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>LVEDVI, ml/m²</td>
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<tr>
<td>LVESVI, ml/m²</td>
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<tr>
<td>Beat volume, ml</td>
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<tr>
<td>Cardiac index, l/min/m²</td>
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<td>Values are median (quartile).</td>
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Abbreviations as in Table 1.
Follow-up outcomes. After surgery, all patients except 1 in the placebo-control group attended a 6-month follow-up visit. Cardiac MRI revealed more significant improvement in the LVEF (change = post-operative value – pre-operative value) in the CABG + BMMNC group than in the placebo-control group (Table 2). As for echocardiographic examination, the changes in the 17-segment wall motion score and the score of segments with abnormal motion were significantly better in the CABG + BMMNC group than in the placebo-control group (Table 3). In the CABG + BMMNC group, the perfusion score decreased significantly, although the difference in the changes in perfusion score did not reach significance level between the 2 groups (Table 4).

Two patients did not take the 6MWT, and 1 patient died during follow-up, leaving 56 patients with available data on the 6MWT. The distance increased more significantly in the CABG + BMMNC group than in the placebo-control group (Table 5). Also, the change in BNP was more significant in the CABG + BMMNC group than in the placebo-control group (Table 6). As for the safety issue, no deaths or MI occurred during follow-up, nor was there any report of arrhythmia during the post-operative period. The proportion of patients who had experienced heart failure did not differ significantly between the 2 groups (3 in each group).

Discussion

To the best of our knowledge, the present study is the first randomized trial assessing the effects of CABG + BMMNCs in patients with PMI complicated by chronic heart failure. It showed that BMMNCs when added to CABG improve LVEF 6 months after CABG, and the score in segments with abnormal motion decreased significantly. The distance of the 6MWT improved more significantly in the CABG + BMMNC group than in the placebo-control group, and serum BNP in the CABG + BMMNC group decreased significantly compared with that in the placebo-control group. All these results indicate that BMMNCs can improve heart function in patients with PMI complicated by chronic heart failure in the short term and might have a positive impact on long-term prognosis and exercise tolerance. The findings of this study add important new evidence to the current debate regarding the value of stem cell therapy for heart failure after MI (6,7,10).

BMMNCs are an ideal cell resource for cell therapy. Previous studies have demonstrated that autologous BMMNCs have the potential to improve heart function by inducing angiogenesis and myocardial regeneration (8,11–13). There are several important subclasses of BMMNCs, such as endothelial progenitor cells, mesenchymal stem cells, and hemopoietic progenitor cells; each type may be capable of improving heart function. Moreover, BMMNCs are easily harvested, and the biological characteristics are largely unaffected when isolated. In our study, in vitro cultured BMMNCs showed good proliferation. No patients had malignant arrhythmia in the present study, indicating that BMMNCs without isolating culture are safe for clinical use.

Traditionally, stem cells are delivered intramyocardially, mostly around the infarcted area, during surgery (2). Although a large number of transplanted cells will stay in situ via the intramyocardial route, a compromising survival rate and impaired proliferation ability are expected when a large number of cells stay in an ischemic or infarcted area. Moreover, the intramyocardially delivered cells are unevenly distributed but recovered and were discharged. No patients had arrhythmia, as defined previously.

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distributed, and some parts where cell therapy is needed are unreachable (14). A previous study revealed that, when delivered via a coronary artery in an arrested heart, a high percentage of transplanted cells will remain within the myocardium of a patient with a PMI (14). In the current study, stem cells were delivered via a graft in an arrested heart. Possibly, abundant lateral branches will enable an even distribution of intragraft-delivered stem cells. Moreover, we hypothesize that, in an arrested heart, capillaries are dilated and vessel permeability is increased so that transplanted cells adhering to the vessel wall will easily migrate to the myocardium. In the present study, the aorta was declamped 5 min after cell injection. This protocol might prolong the contact time between BMMNCs and a microcoronary artery, enhance the adhering ability of BMMNCs, and consequently decrease the number of BMMNCs washed out of the heart (15).

Compared with other studies of CABG combined with stem cell therapy (11,12), the current study controlled patient selection rigorously to only include those with triple-vessel disease, PMI, and chronic heart failure. Moreover, the candidates were not eligible for this study unless they underwent isolated CABG (refers to those receiving CABG only). Also, we took great care to control confounding factors arising from surgery, such as the type of CABG techniques and the surgeons.

Study limitations. This study is, however, not without its limitations. The number of patients involved is still small and compared with positron emission tomography/computed tomography, the resolution of SPECT imaging used in our study was relatively low, which could lead to false-negative findings. We did find the that imaging in parts of patients was unclear, and analysis was almost impossible. Moreover, our current Siemens scanner could not provide accurate quantitative data about infarction size. Our study was designed to focus on the effects of stem cells effects on global heart function instead of MI size.

Conclusions

In summary, patients with PMI and chronic heart failure could potentially benefit from isolated CABG combined with BMMNCs delivered via a graft vessel. The LVESVI decreased, LVEF increased, and the exercise tolerance improved during follow-up. Further large randomized trials are needed to assess the effects of BMMNCs on the long-term prognosis of patients using more clinically meaningful outcomes.

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REFERENCES