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Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up‡

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Aims To evaluate the safety profile and efficacy of bone marrow mononuclear cells (BMMNC) transplantation for ST-segment elevation myocardial infarction (STEMI) by assessing patients and their left ventricular function at up to 4 years follow-up.

Methods and results Eighty-six patients with STEMI who had successfully undergone percutaneous coronary intervention (PCI) were randomized to receive intracoronary injection of BMMNC ($n = 41$) or saline ($n = 45$). Left ventricular ejection fraction, as evaluated by UCG, was markedly improved at 6 months (0.484 ± 0.5 vs. 0.457 ± 0.6, $P = 0.001$), 1 year (0.482 ± 0.7 vs. 0.446 ± 0.6, $P < 0.001$), and 4 years (0.505 ± 0.8 vs. 0.464 ± 0.8, $P < 0.001$) after BMMNC transplant when compared with control group. However, the current cell therapy did not improve the myocardial viability of the infarcted area as assessed by single-photon emission computed tomography analysis at 4 years post-transplant (0.263 ± 0.007 in BMMNC group vs. 0.281 ± 0.008 in control group, $P = 0.10$). During the follow-up period, one control group case (2.2%) of in-stent restenosis was confirmed by coronary angiography and underwent repeat PCI. Also during follow-up, one death (2.2%) occurred in the control group, and one patient (2.4%) in the BMMNC group had transient acute heart failure.

Conclusion This study indicates that intracoronary delivery of autologous BMMNC is safe and feasible for STEMI patients who have undergone PCI, and can lead to long-term improvement in myocardial function.

Keywords Bone marrow mononuclear cells • Cell therapy • ST-segment elevation myocardial infarction • Percutaneous coronary intervention • Left ventricular function

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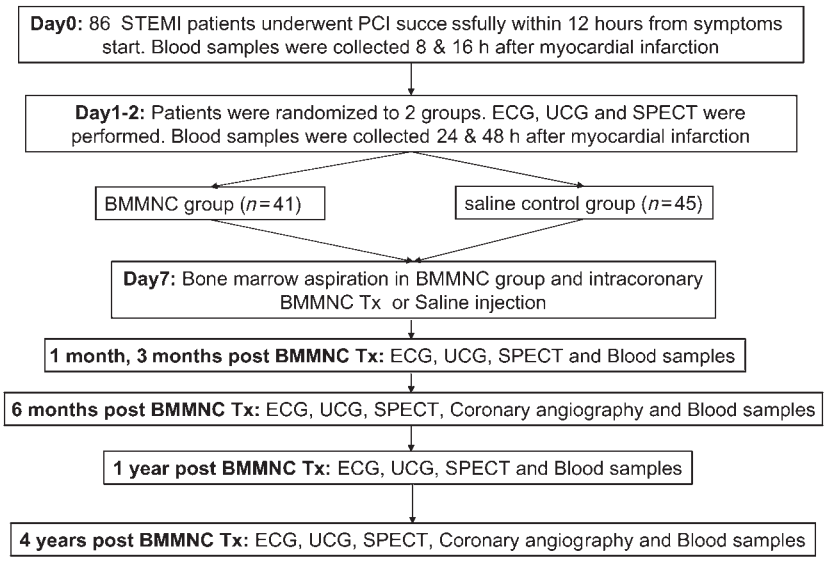

Figure 1 Flowchart outlining the study protocol.

Introduction

Acute myocardial infarction (AMI) resulting from atherosclerotic obstruction or arterial narrowing remains the leading cause of morbidity and mortality worldwide.[1,2] Current therapies for AMI such as percutaneous coronary intervention (PCI) can localize the AMI-affected area, normalize coronary perfusion, and enable viable ischaemic tissue to recover, thus limiting further necrosis. However, many patients develop left ventricular (LV) remodelling and progressive heart failure after AMI. The restoration of cardiac function in such situations remains a major challenge.

Stem cells are capable of the important properties of self-renewal and differentiation plasticity.[3,4] Human autologous bone marrow mononuclear cells (BMMNC) contain $CD34^+$ haematopoietic and $CD34^-$ mesenchymal stem cells.[5] Both of these cell types may contribute to heart muscle repair in AMI. In recent years, a variety of clinical trials have explored the hypothesis that BMMNC transplantation may enhance the recovery of LV function after AMI.[6,7] The use of BMMNC is clinically justified and ethically unquestionable because no severe side effects have been reported, and immunosuppressive therapy is unnecessary. However, most clinical trials of BMMNC transplantation for AMI patients are short-term observations with rare reports of long-term follow-up results. The aim of the present study was to investigate the efficacy of and LV functional improvement after BMMNC transplantation in patients with ST-segment elevation myocardial infarction (STEMI) at up to 4 years follow-up.

Methods

Patient population

Eighty-six STEMI patients with the culprit lesion in the left anterior descending artery proximal to the two diagonal branches were enrolled consecutively between July 2003 and March 2004. Patients were treated by acute PCI successfully within 12 h of the onset of symptoms. The study protocol was approved by the Ethics Committee of Fourth Military Medical University. All of the patients gave written, informed consent. An independent data and safety monitoring board was informed of adverse events as they occurred.

Inclusion criteria were age between 40 and 65 years old, STEMI according to the WHO definition, PCI <12 h from the onset of symptoms, one vessel disease with an open infarct related artery amenable to cell therapy. General exclusion criteria were previous MI, cardiomyopathy, atrial fibrillation or flutter, previous heart surgery, severe valvular heart disease, disease of the haematopoietic system, NYHA functional class IV heart failure at baseline, severe renal, lung and liver disease or cancer, significant coronary lesion in one or more major coronary vessels, intracardiac thrombus, and bone marrow disease.

Study design and baseline evaluation

The study design is shown in *Figure 1*. A detailed history was recorded. Creatinine phosphokinase (CK), MB isoenzyme of creatinine kinase (CK-MB), homocysteine, prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (FIB), international normalized ratio (INR), urea nitrogen (UN), creatinine, routine blood tests, blood cholesterol, blood glucose, and blood pressure were recorded on the day of admission to the hospital. All of the patients received medication in accordance with current guidelines for the management of patients with STEMI.[8] Patients were randomized to the BMMNC group ($n = 41$) or saline group ($n = 45$) as follows: random numbers between 0 and 1 were generated and a median value was calculated. Random numbers greater than the median value were allocated to the BMMNC group. Consecutively numbered, sealed envelopes were provided by the clinical research centre of Xijing Hospital. Blood samples were collected. ECG, UCG, single-photon emission computed tomography analysis (SPECT), and coronary angiography data were collected. Cumulative major adverse cardiac events (MACE), including cardiac death, non-fatal myocardial infarction, and target lesion revascularization, were also recorded.

Bone marrow aspiration and isolation of bone marrow mononuclear cells

Bone marrow (40 mL) aspiration was conducted 7 days after successful PCI under local anaesthesia. Density gradient centrifugation was used to isolate BMMNC. In brief, the bone marrow solution was gently added onto 10 mL Ficoll (Lymphoprep^{TM}, Axis-Shield, Norway, density 1.073) and centrifuged at 900 *g* for 30 min at room temperature. The mononuclear cell layer was harvested and washed three times before final resuspension in 10 mL heparinized saline. The final preparation of the injected cells contained $5 \pm 1.2 \times 10^7$ mononuclear cells per millilitre. Cell viability was 96 ± 3.2% and $CD34^+$ cell fraction was 1.8 ± 0.6%.

Bone marrow mononuclear cells delivery

After acquiring routine PCI access, an over-the-wire balloon catheter was advanced to the proximal part of the stented culprit lesion and inflated with four to five ATM for 1 min to occlude blood flow. At the same time, 2.5 mL of cell suspension containing $\sim 1.25 \times 10^8$ BMMNC was injected into the infarct-related coronary artery. This procedure was repeated four times. The control group did not undergo bone marrow aspiration and was injected with the same volume of heparinized saline as the BMMNC groups.

Echocardiographic evaluation of left ventricular function

Echocardiogram was recorded using a HDI 5000 scanner and an iE 33 scanner (Philips Ultrasound, Washington, DC, USA). Four consecutive cineloops of four apical views were recorded to analyse LV volumes. End-systolic volume (ESV), end-diastolic volume (EDV), and left ventricular ejection fraction (LVEF) were calculated using the modified Simpson's rule according to current guidelines.[9] Wall motion score index (WMSI) was measured by segment score calculation. Two experienced ultrasound technicians unaware of treatment allocation processed all recordings. If a discrepancy between the readings of >5% was noted, a third blinded observer was called and a consensus achieved.

Quantitative single-photon emission computed tomography analysis

ECG-gated SPECT imaging was performed as follows at baseline and at follow-up. Approximately 740–925 MBq (weight-adjusted) of 99 m Technetium (HTA Co., Ltd, China) was injected at rest. An hour later, SPECT imaging was initiated, using a 15% window centred over the 140 keV photopeak. Acquisitions were performed with a two-detector SPECT (Hawkeye, GE). An Entegra (GE Medical Systems) processing station was used for processing of all recordings and assessment of LV volumes and infarct size (proportion perfusion defect). Two experienced nuclear medicine technicians who were blinded to the treatment allocation processed all recordings. If a discrepancy between the readings of >5% was noted, a third blinded observer was called and a consensus achieved.

Quantification of coronary artery restenosis

Quantitative coronary angiography (QCA) was evaluated and performed with GE QCA software (GE Innova 2000, Fairfield, CT, USA). Coronary artery restenosis was defined as more than 50% loss of luminal diameter within stents at follow-up.

Statistical analysis

Continuous variables that approximated the normal distribution were expressed as mean ± SD or mean ± SEM. Comparison between the BMMNC and the control group was made using repeated-measures ANOVA. A two-sample *t*-test was performed for comparison between groups in a specific time point. Comparisons between different time points during the follow-up periods in the same group were performed by a paired *t*-test. Categorical parameters were presented as proportion or number. Differences between groups were assessed with the χ^2 test or Fisher's exact test, as appropriate. Two-sided tests have been used throughout, and *P*-values less than 0.05 were considered statistically significant. SPSS software package version 14.0 (SPSS, Chicago, IL, USA) was used for data analysis.

Results

Baseline comparison and safety evaluation of procedure by myocardial enzyme assay and major adverse cardiac events

Eighty-six patients were included in the study. There were no major differences between the two groups in terms of patient characteristics (*Table 1*). After intracoronary transplantation of BMMNC, no statistically significant changes were found on CK, CK-MB, homocysteine, PT, TT, APTT, FIB, INR, UN, creatinine, routine blood tests, blood cholesterol, blood glucose, blood pressure or ECG tests (data not shown). One case (2.2%) of in-stent restenosis in the control group was confirmed by coronary angiography and was subjected to repeat PCI at 1 year follow-up. One patient (2.4%) had transient acute heart failure in the BMMNC group 7 days after cell transplantation and one death (2.2%) occurred in the control group at 1 year follow-up. No acute or long-term adverse effects in terms of proarrhythmia, tumour formation, or intramyocardial calcification were observed.

Echocardiography evaluation

Left ventricular ejection fraction, WMSI, ESV, and EDV were evaluated by echocardiography (*Table 2*). Left ventricular ejection fraction improved in both the BMMNC and the control group during the follow-up period. The LVEF measured at 6 months (0.484 ± 0.5 vs. 0.457 ± 0.6, $P = 0.001$), 1 year (0.482 ± 0.7 vs. 0.446 ± 0.6, $P < 0.001$), and 4 years (0.505 ± 0.8 vs. 0.464 ± 0.8, $P < 0.001$) follow-up was increased significantly in the BMMNC group when compared with the control group (*Figure 2B*). End-systolic volume decreased in both the BMMNC and the control group. End-systolic volume measured at 6 months (60.9 ± 0.8 mL vs. 66.3 ± 1.2 mL, $P < 0.001$), 1 year (60.3 ± 1.1 mL vs. 67.0 ± 1.3 mL, $P < 0.001$), and 4 years (60.9 ± 1.4 mL vs. 67.2 ± 1.5 mL, $P = 0.003$) follow-up was significantly decreased in the BMMNC group when compared with controls (*Figure 2C*). Wall motion score index was also decreased in both the BMMNC and the control group. Comparison between the two groups at 6 months (1.43 ± 0.01 vs. 1.48 ± 0.02, $P = 0.04$), 1 year (1.35 ± 0.02 vs. 1.41 ± 0.02, $P = 0.02$), and 4 years (1.23 ± 0.01 vs. 1.37 ± 0.03, $P < 0.001$) after cell or standard therapy demonstrated significant differences in WMSI according to the regional wall motion analysis. No significant differences of EDV were observed between the two groups.

There was a statistically significant increase in LVEF between day 7 and 4 years post-MI when comparing the BMMNC group with

Table 1 Characteristics of the patients

Characteristics	BMMNC ($n = 41$)	Control ($n = 45$)	*P*-value
Male (%)	95.1	93.3	1.0
Age (year)	50.7 ± 1.1	51.0 ± 1.0	0.85
Hypertension (%)	48.8	44.4	0.69
Hyperlipidaemia (%)	36.6	35.6	0.92
Diabetes mellitus (%)	24.4	26.7	0.81
Current smoker (%)	61.0	62.2	0.91
UN (mmol/L)	4.2 ± 0.1	4.0 ± 0.1	0.25
Cr (μmol/L)	56.2 ± 2.3	57.8 ± 2.4	0.65
CK peak value (U/L)	3271.1 ± 275.2	3521.9 ± 275.5	0.52
CK-MB peak value (U/L)	347.6 ± 21.6	375.9 ± 24.8	0.40
Symptom to balloon time (h)	6.5 ± 0.3	6.8 ± 0.3	0.55
Stent number (total)	47	50	0.29
Angioguard TM (total)	9	8	0.29
Killip class			0.61
I	15	18	
II	22	20	
III	4	7	
Drug-eluting stents (%)	85.4	77.8	0.37
Medication			
Aspirin (%)	100	100	1.0
Clopidogrel (%)	100	100	1.0
ACE-I/ARB (%)	100	100	1.0
β-Blocker (%)	95.1	95.6	1.0
Statin (%)	100	100	1.0

Values are presented as mean ± SEM or number or proportion.

the control group [mean change 3.5% (CI 95%, 1.4–5.5)%, $P = 0.001$] (*Figure 2D* and *E*). Also, the reduction in ESV was significantly greater in the BMMNC group when compared with the control group over the 4 years study period [mean change −7.6 mL (CI 95%, −11.9 to −3.3 mL), $P < 0.001$] (*Figure 2F* and G). There was no significant difference between groups in terms of EDV change [mean change −5.9 mL (CI 95%, −12.4 to 0.7 mL), $P = 0.08$] (*Figure 3A* and *B*). The change in WMSI was also significantly higher in BMMNC group than in control group [mean change −0.16 (CI 95%,−0.24 to −0.08), $P < 0.001$] (*Figure 3C* and *D*).

Single-photon emission computed tomography analysis evaluation

Infarct size, LVEF, ESV, and EDV were evaluated by SPECT. Infarct size decreased in both the BMMNC and the control groups (*Figure 4A* and *B*), although comparison of infarct size between the two groups showed no statistical difference at 4 years post-transplant (0.263 ± 0.007 in BMMNC group vs. 0.281 ± 0.008 in control group, $P = 0.10$). (*Figure 4C*). Changes in infarct size

Table 2 Left ventricular ejection fraction, end-systolic volume, end-diastolic volume, and wall motion score index evaluated by echocardiography at baseline and follow-up period

	LVEF (%)		ESV (mL)		EDV (mL)		WMSI	
	BMMNC ($n = 41$)	Control ($n = 45$)	BMMNC ($n = 41$)	Control ($n = 45$)	BMMNC ($n = 41$)	Control ($n = 45$)	BMMNC ($n = 41$)	Control ($n = 45$)
Day 0	39.0 (3.0, 0.5)	38.6 (3.0, 0.5)	74.1 (7.4, 1.2)	74.1 (8.4, 1.2)	122.3 (11.4, 1.8)	121.5 (11.6, 1.8)	1.77 (0.15, 0.02)	1.80 (0.18, 0.03)
Day 7	41.3 (2.8, 0.4)	40. 7 (3.1, 0.5)	73.1 (6.3, 1.0)	71.8 (7.4, 1.1)	125.5 (10.0, 1.6)	121.9 (11.1, 1.7)	1.71 (0.19, 0.03)	1.68 (0.12, 0.02)
1 Month	43.5 (3.2, 0.5)	42.3 (3.2, 0.5)	69.0 (5.3, 0.8)	70.3 (8.8, 1.3)	123.0 (7.1, 1.1)	122.4 (12.4, 1.9)	1.60 (0.19, 0.03)	1.59 (0.10, 0.01)
3 Months	44.9 (3.1, 0.5)	43. 5 (3.7, 0.6)	66.0 (8.3, 1.3)	68.2 (7.5, 1.1)	120.6 (12.8, 2.0)	121.3 (10.2, 1.5)	1.54 (0.13, 0.02)	1.54 (0.10, 0.02)
6 Months	48.4 (3.5, 0.5)*	45. 7 (3.9, 0.6)	60.9 (5.1, 0.8)*	66.3 (7.8, 1.2)	119.1 (7.9, 1.2)	123.0 (10.7, 1.6)	1.43 (0.07, 0.01)*	1.48 (0.11, 0.02)
1 Year	48.2 (4.4, 0.7)*	44.6 (4.3, 0.6)	60.3 (6.9, 1.1)*	67.0 (8.4, 1.3)	117.2 (8.3, 1.3)	121.9 (13.0, 1.9)	1.35 (0.10, 0.02)*	1.41 (0.14, 0.02)
4 Years	50.5 (5.0, 0.8)*	46.4 (5.2, 0.8)	60.9 (9.0, 1.4)*	67.2 (9.9, 1.5)	124.2 (12.4, 1.9)	126.4 (14.0, 2.1)	1.23 (0.08, 0.01)*	1.37 (0.18, 0.03)

Values are presented as mean (SD, SEM); LVEF, left ventricular ejection fraction; ESV, end-systolic volume; EDV, end-diastolic volume; WMSI, wall motion score index.
*$P < 0.05$ vs. Control.

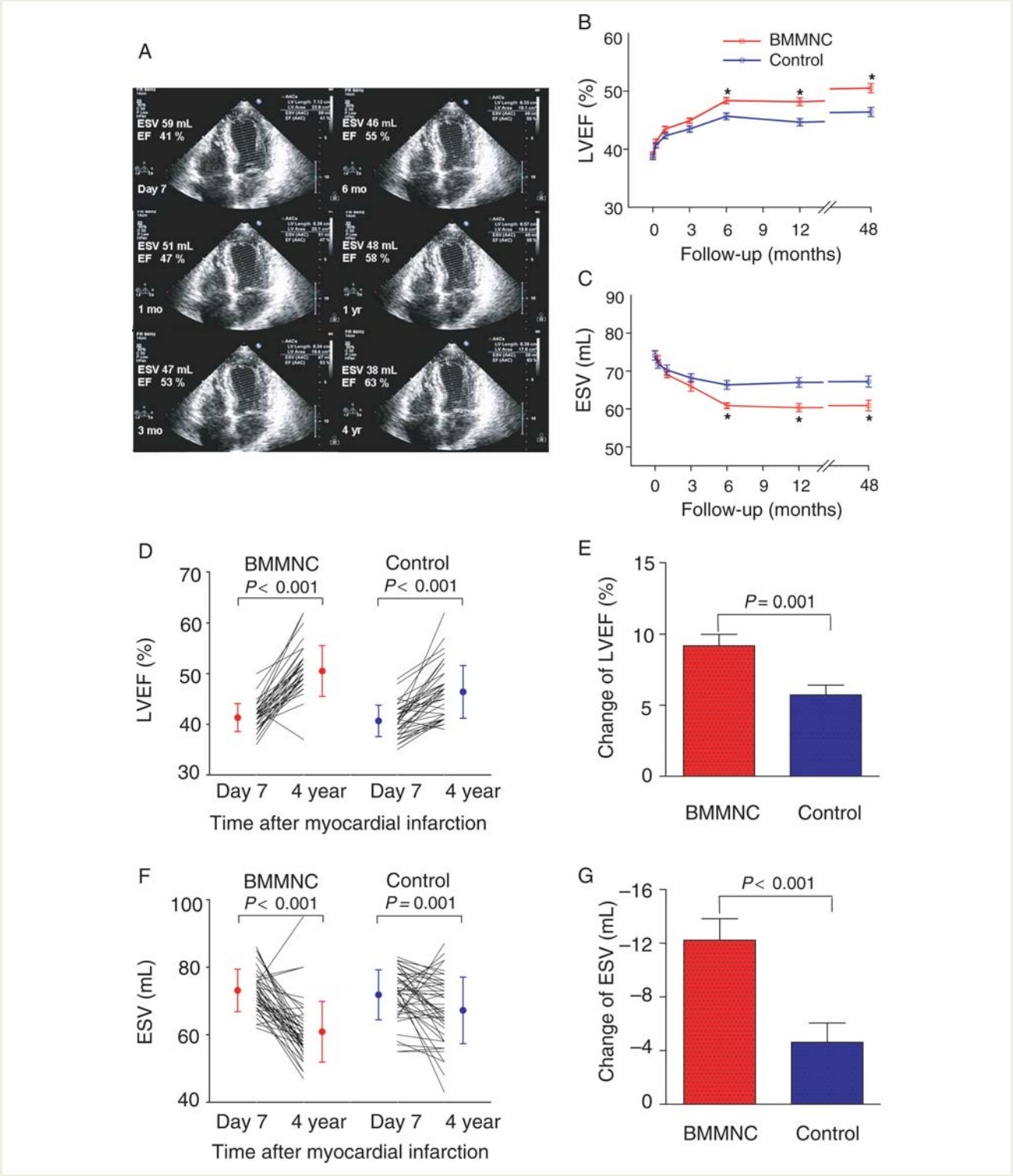

Figure 2 Improvement of LVEF and ESV evaluated by echocardiography. LVEF and ESV changes were recorded in a representative patient from baseline (Day 7) to 4 years after MI. (*A*) LVEF measured at 6 months, 1 and 4 years' follow-up was increased significantly in the BMMNC group when compared with the control group (*B*). ESV in the BMMNC group was decreased significantly more than in the control group at 6 months, 1 and 4 years follow-up (*$P < 0.05$ vs. control) (*C*). Changes in LVEF and ESV between Day 7 and 4 year were significant in the BMMNC group (*D*–*G*). LVEF, left ventricular ejection fraction; ESV, end-systolic volume. Solid circles represent the mean, T bars the standard error (SE).

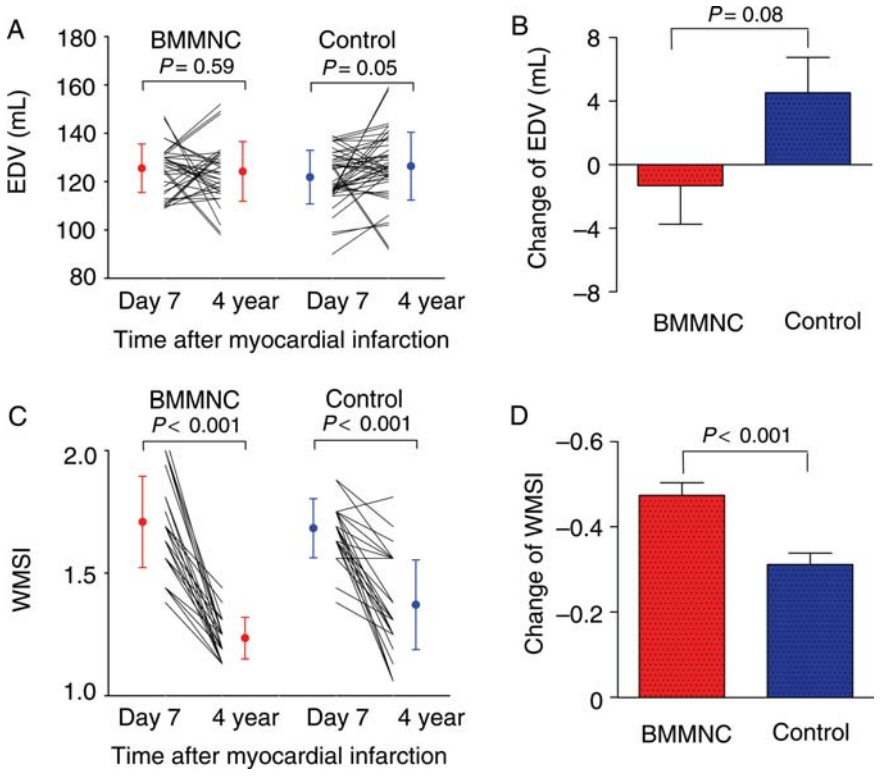

Figure 3 Changes of EDV and WMSI between Day 7 and 4 years after the myocardial infarction evaluated by echocardiography. Changes in EDV between Day 7 and 4 year were not significantly different between the two groups (*A* and *B*). WMSI improved significantly in the BMMNC group compared with control (*C* and *D*). EDV, end-diastolic volume; WMSI, wall motion score index. Solid circles represent the mean, T bars the standard error (SE).

between day 7 and 4 yr also showed no significant difference between the two groups ($-9.5 \pm 0.9\%$ in BMMNC group vs. $-7.1 \pm 0.9\%$ in control group, $P = 0.06$) (*Figure 4D*). Measurements of LVEF, ESV, and EDV showed similar trends to those found with echocardiography (data not shown).

Subgroup analysis

Data obtained by echocardiography were subjected to subgroup analysis. Changes in LVEF between baseline (Day 7) and 4 years were greater in non-diabetic patients when compared with diabetic patients [BMMNC: $(9.7 \pm 5.6)\%$ vs. $(7.6 \pm 2.8)\%$, $P = 0.26$; Control: $(6.7 \pm 4.8)\%$ vs. $(3.0 \pm 2.5)\%$, $P = 0.01$] (*Figure 5A*). Also, patients aged less than 50 had a greater improvement in LVEF between baseline and 4 years when compared with patients with age 50 or more [BMMNC: $(10.5 \pm 3.3)\%$ vs. $(8.0 \pm 6.2)\%$, $P = 0.11$; Control: $(7.7 \pm 4.8)\%$ vs. $(4.2 \pm 3.8)\%$, $P = 0.01$] (*Figure 5B*). Subgroup analysis also evaluated patients with hypertension and hyperlipidaemia, and the changes in LVEF were not consistent either the BMMNC and the control group (*Figures 5C* and *D*).

Discussion

The efficacy of stem cell transplantation has been demonstrated by many animal and clinical studies.[7,10] Different cell types have been proposed for cardiac regeneration, including embryonic stem cells, skeletal myoblasts, endothelial progenitor cells, and BMMNC.[11–13] In these cell types, BMMNC have gained attention as an easily accessible, homogeneous cell population for cardiac repair.

Although compelling evidence suggests that intracoronary transplantation of BMMNC can help to enhance the recovery of heart function after AMI,[6,7,14] the efficacy of BMMNC transplantation remains controversial. More recently, several meta-analyses evaluating the impact of intracoronary cell therapy on AMI concluded that stem cell therapy improved LVEF and significantly reduced ESV and myocardial lesion area.[15–17] Of note, the maximal follow-up period in these studies was 18 months. In the present study, stem cell therapy improved LVEF by 3.5% when compared with controls over a 4 years follow-up period. However, the current cell therapy did not further improve the myocardial viability of the infarcted area as assessed by SPECT 4 years after transplantation. These results show that BMMNC transplantation promotes left ventricle contraction significantly and persistently without potent effects on angiogenesis.

Several mechanisms may underlie LV function improvement in patients who underwent cell therapy. Reyes *et al.*[13] have previously found that BM cells have the potential of integrating into the syncytium of host cardiac myocytes and transdifferentiating into either myocardial or vascular cells. Induction of cell fusion between BMMNC and resident myocytes has also been documented in other studies.[18–21] Although the present study does not provide

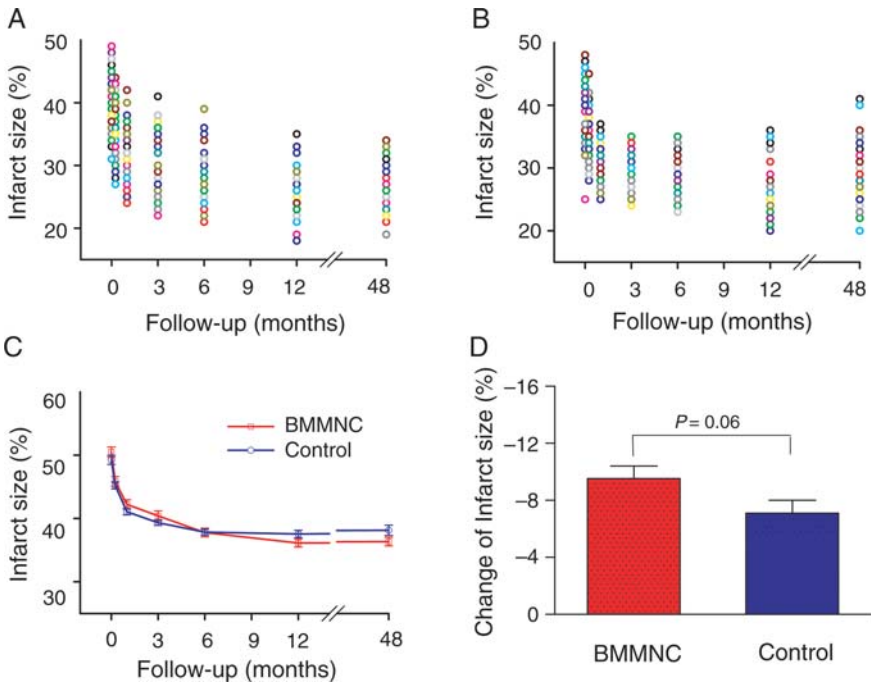

Figure 4 Infarct size evaluated by single-photon emission computed tomography analysis (SPECT). Infarct size decreased in both the bone marrow mononuclear cells (BMMNC) and the control group (*A* and *B*). Comparison of infarct size between the two groups showed no statistical difference (*C*). Changes in infarct size between Day 7 and 4 years follow-up were not significantly different between the two groups (*D*).

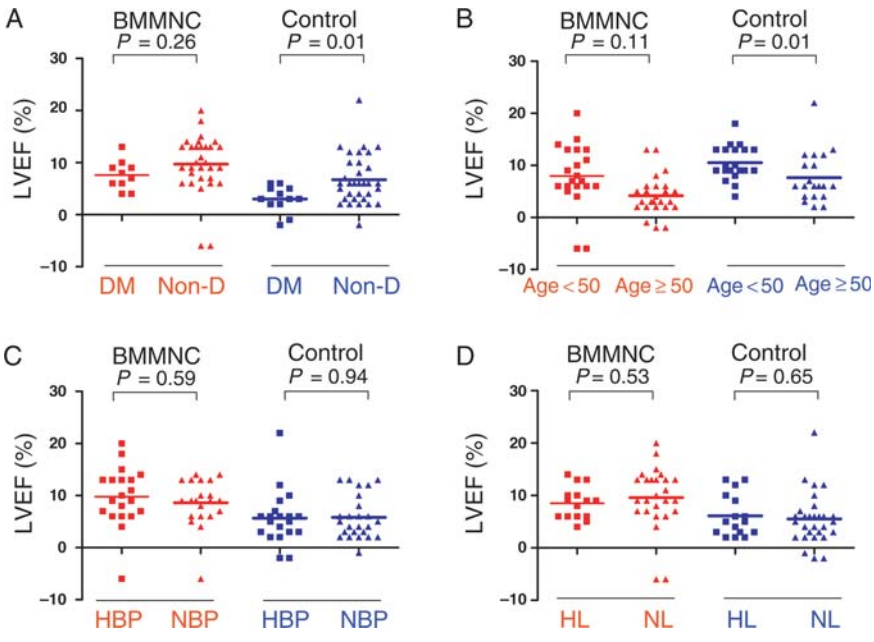

Figure 5 Subgroup analysis. Principle transverse lines represented the mean changes in left ventricular ejection fraction (LVEF) between baseline and 4 years follow-up. DM, diabetes mellitus; Non-D, non-diabetic patients; HBP, high blood pressure; NBP, normal blood pressure; HL, hyperlipidaemia; NL, normal lipidaemia.

evidence that BMMNC can or cannot differentiate into myocytes or endothelial cells, the significant improvement of LVEF suggests the possibility of paracrine effects of BMMNC. Numerous studies have demonstrated that BMMNC are capable of releasing multiple growth factors including vascular endothelial growth factor, stromal cell-derived factor-1, insulin-like growth factor, and platelet-derived growth factor.[22–25] More recent data show that BMMNC deliver a distinct cocktail of growth factors and cytokines into infarcted myocardium. These data and the present study indicate that further characterization of the BMMNC secretome may lead to the identification of factors with therapeutic potential after AMI.[26] These growth factors may intensify ventricular wall movement, improve LVEF, and delay LV dilation.

In our study, no changes were found in CK, CK-MB, homocysteine, PT, TT, APTT, FIB, INR, UN, creatinine, routine blood tests, blood cholesterol, blood glucose or blood pressure levels, or ECG data after BMMNC delivery. No acute or long-term adverse effects, such as proarrhythmias, tumour formation, or intramyocardial calcification were observed. These results differed from those of Villa *et al.*[27] and Solheim *et al.*[28] Bone marrow mononuclear cells transplantation-based clinical trials have been rife with concerns regarding the safety and side effects of intracoronary delivery, including potential cardiac risks such as arrhythmia, calcification, inflammation, and extracardiac risks such as tumour, infection, and liver/kidney dysfunction. However, the use of intracoronary cell infusion continues to be a popular approach, given the familiarity of most cardiologists with this well-established procedure. Our present study demonstrated rare obvious cardiac side effects and no major extracardiac event, such as tumour or infection, in both groups during the 4 years follow-up. These results concur with those of the meta-analysis published by Martin-Rendon *et al.*[16] On the basis of our previous studies on stem cell delivery in small animals,[29] we find molecular imaging techniques to be the ideal tools to further assess cellular therapy systematically *in vivo*. The results of the present study clearly suggest the importance of further detailed study in tracking cells and assessing *in vivo* function in the context of intracoronary, intramyocardial, interstitial retrograde coronary venous, or other delivery approaches in human clinic trials.

During the follow-up period, one case (2.2%) of in-stent restenosis in the control group was confirmed by coronary angiography and subjected to repeat PCI at 1 year follow-up. One patient (2.4%) in the BMMNC group had transient acute heart failure 7 days after cell transplantation and one death (2.2%) occurred in the control group at 1 year follow-up. When compared with other studies, the rate of adverse events in this study was relatively low. This may due to our enrolment of patients around the age of 50 and strict inclusion criteria defining low-risk patients. The high rate of drug-eluting stent implantation (85.4% in BMMNC group vs. 77.8% in control group) is another potential reason for the low rate of adverse events. Although the incidence of MACE was not statistically different between groups, LV function was improved significantly in the BMMNC group. In order to further demonstrate the efficacy of BMMNC intervention, exercise capacity and quality of life should be measured in future studies.

In order to identify patients who benefit most from stem cell therapy, subgroup analysis was performed. Changes in LVEF between baseline (Day 7) and 4 years were consistently greater in non-diabetic patients and with patients aged less than 50 in both the BMMNC group and the control group. Although the current population was too small to obtain statistically significant differences, the results indicated that younger patients or patients without diabetes mellitus may benefit more from stem cell therapy.

In this study, we did not purify isolated BMMNC into a single cell population such as mesodermal progenitor cells, haematopoietic progenitor cells, and endothelial progenitor cells, because we are currently unable to determine which cell type is responsible for myocardial functional improvement. Bone marrow mononuclear cells containing different cell types may represent an ideal cell source for treating different diseases by exerting various protective effects.[2] A large number of clinical trials have been published demonstrating the effectiveness of unfractionated BMMNC in various clinical conditions including AMI, chronic coronary artery disease, non-ischaemic dilated cardiomyopathy, and chronic ischaemic heart failure.[6,7,30–32]

The present controlled study indicated that intracoronary transplantation of BMMNC is safe and feasible for STEMI patients who have undergone PCI and that such treatment can lead to long-term myocardial functional improvement. The possible mechanisms of such an outcome include paracrine effects of BMMNC. However, a detailed explanation delineating the specific cell type and molecular mechanism responsible for the observed restorational effect will require more dedicated investigation.

Study limitations

Sample size in the present study was small, so large-scale clinical trials need to be performed to verify the generalizability of the present conclusion. Owing to a lack of approved tracking methods that are safe and applicable in human beings, the survival, proliferation, and migration of BMMNC could not be visualized after transplantation. Therefore, the development of 'molecular markers' that can monitor the fate of transplanted BMMNC will be extremely useful in future studies.[33] In addition, BMMNC contain a variety of cell types. The detailed mechanism and specific cell type responsible for myocardial functional improvement remains to be clarified.

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