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Long-Term Outcome of Intra-Myocardial Injection of Autologous Bone Marrow Mononuclear Cells Combined with Isolated Coronary Artery Bypass Grafting for Patients with Chronic Ischemic Heart Failure

Rong Wang, MD,* Lin Zhang, MD,* Yao Wang, MD, Zhiyun Gong, MD, Cangsong Xiao, MD, Yang Wu, MD, Chonglei Ren, MD, Nan Cheng, MD, Changqing Gao, MD*

Department of Cardiovascular Surgery, Chinese People's Liberation Army General Hospital, Institute of Cardiac Surgery, Beijing, China

ABSTRACT

Objective: This study aimed to investigate whether intra-myocardial injection of autologous bone marrow mononuclear cells (aBMMNCs) into peri-scarred myocardium during coronary artery bypass grafting (CABG) improved the long-term outcome compared with CABG alone.

Methods: From April 2011 to December 2012, 33 patients with chronic ischemic heart failure were randomly assigned to undergo CABG (control group) or CABG combined with intra-myocardial injection of aBMMNCs (treatment group). The primary endpoints of the study were the changes of left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) from baseline to six-month and two-year follow-up, respectively. The secondary endpoints were the changes of III and IV NYHA classification, 6-minute walk test, B-type natriuretic peptide (BNP) from baseline to follow-up, and major adverse cardiovascular events (MACES) during the follow-up.

Results: No patient died and no severe surgical complication occurred perioperatively in either group. The mean number of transplanted aBMMNCs was 98.5 ± 48.3×10^6 per patient. The follow-up was completed at six months and 24 months postoperatively. No major transplant-related adverse events were detected during the study. The patients in the treatment group had more significant improvement in LVEF than in the control group at six-month follow-up (8.17% versus 4.71%, P = .020), but this benefit was not found at 24-month follow-up (7.44% versus 5.69%, P = .419). There was no significant difference in changes of LVEDV, LVESV, III and IV NYHA classification, 6-minute walk distance, BNP, and MACES between the two groups all through the study.

Conclusion: Intra-myocardial injection of aBMMNC transplantation on arrested heart during CABG is a safe procedure based on a longer period observation. The patients with chronic ischemic heart failure can benefit from aBMMNCs transplantation in the short-term (6 months) demonstrated by improved global LVEF compared with the control group; however, this additional benefit dimed with time as showed by 24-month clinical and echocardiographic follow-up results.

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**These authors contributed equally to this work.*

Correspondence: Changqing Gao, Department of Cardiovascular Surgery, Chinese PLA General Hospital, 28 Fuxing Road, Beijing, China 100853; +8601066938035; fax: +8601066938035 (e-mail: gaochq301@hotmail.com).

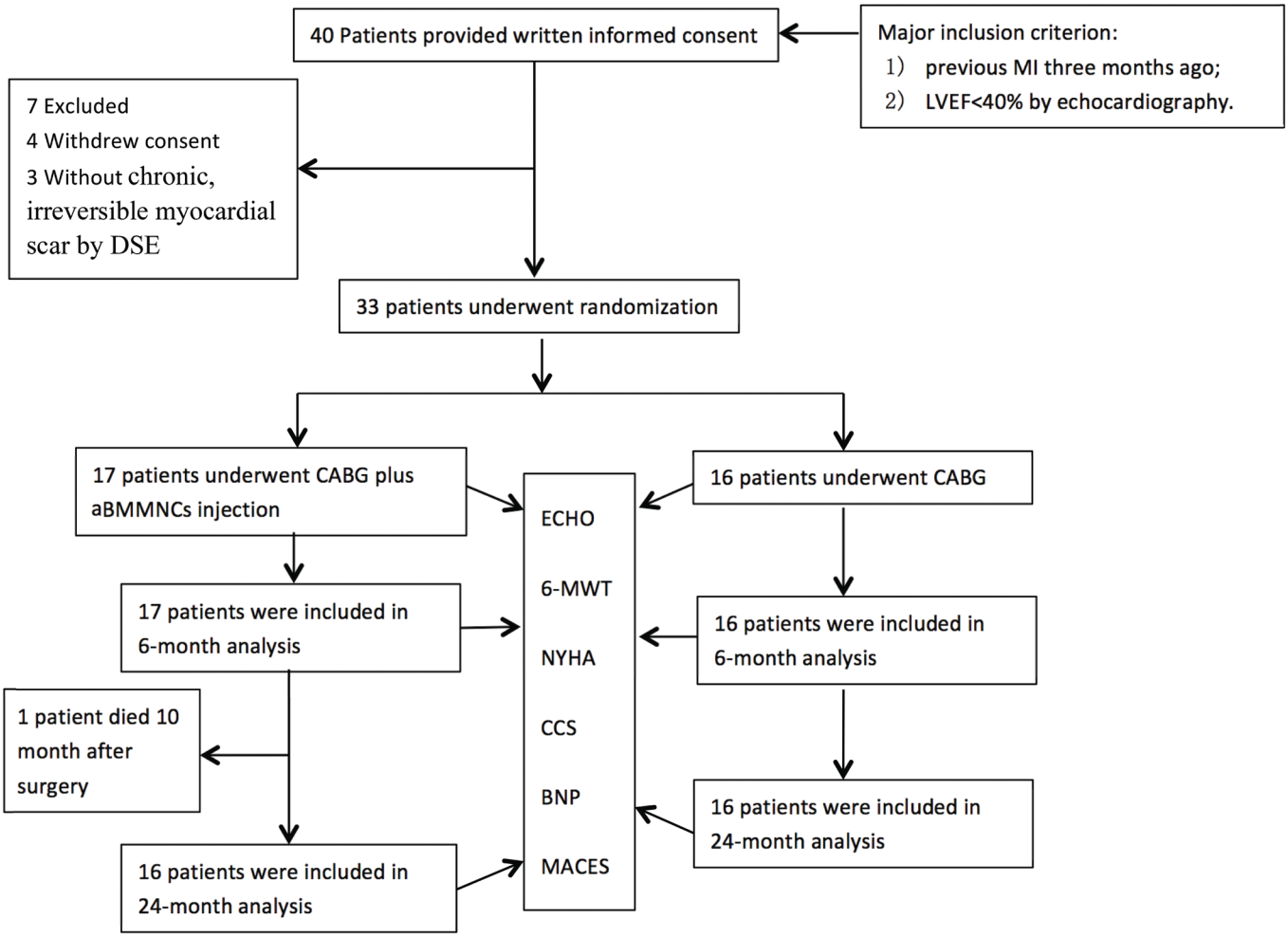
INTRODUCTION

Heart failure (HF) is a worldwide public health problem and ischemic heart disease is the most common cause of HF in the world [Mozaffarian 2015]. Almost 60% of patients in the ADHERE Registry study had a history of coronary artery disease and about 68% of patients enrolled in chronic HF clinical trials had ischemic heart disease recorded as their HF etiology [Adams 2005; Gheorghiade 1998]. Ischemic HF often develops after myocardial infarction (MI), resulted from large areas of cardiomyocyte loss. Therefore, stem cell therapy has been introduced clinically as a promising treatment for severe ischemic HF in recent years. Dozens of randomized clinical trials have been implemented and aBMMNCs combined with interventional or surgical revascularization was testified as safe, easy to harvest, simple to administer, ethically acceptable, and without a requirement of immunosuppression [Mocini 2006; Beeres 2007; Zhao 2008; van Ramshorst 2009; Hu 2011; Suzuki 2004; Lunde 2006; Cao 2009; Hirsch 2011; Traverse 2012; Gyongyosi 2009; Assmus 2002]. Previous studies have shown global or regional improvement of left ventricular function after aBMMNCs transplantation into peri-infarcted areas in patients with chronic ischemic heart failure in short-term follow-up [Donndorf 2011]. However, the long-term results were scarce and controversial [Patila 2014]. Thus, we performed this randomized, controlled clinical study to investigate whether administration of aBMMNCs by intramyocardial injection during CABG was safe and improve cardiac function compared with CABG alone in the long-term. The study was approved by the local ethics committee (the Chinese PLA General Hospital) and was conducted in accordance with the Declaration of Helsinki.

MATERIALS AND METHODS

Study Population

From April 2011 to December 2012, patients aged 18-75 years with chronic ischemic heart failure were considered



Study design, enrollment, and outcomes. 33 patients entered the current study. They were then randomized into the CABG + aBMMNCs group and the control group. DSE indicates dobutamine stress echocardiography; aBMMNCs, autologous bone marrow mononuclear cells; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; MI, myocardial infarction; ECHO, echocardiography; 6MWT, 6-min walking test.

for the study. The major inclusion criteria were as follows: 1) coronary artery disease with history of previous MI longer than three months; 2) LVEF < 40% by echocardiography; 3) isolated elective CABG for triple-vessel disease according to American Heart Association guidelines; 4) the presence of at least one chronic, irreversible myocardial scar defined as areas of akinesia or dyskinesia with no contractile reserve on dobutamine stress echocardiography (DSE); and 5) without left ventricular aneurysm or valvular heart diseases requiring concomitant surgical intervention.

Exclusion criteria were combined severe valvular heart disease or left ventricular aneurysm requiring concomitant surgery, emergent condition, hepatic or renal dysfunction, evidence of malignancy, active infection, preexisting bone marrow diseases, preexisting ventricular tachycardia, and prior cardiac surgery.

All participants gave written informed consent at enrollment and received the same standard medical treatment and rehabilitation regiments as other patients undergoing standard CABG.

Study Design

40 patients entered the screening process and 7 were excluded due to different reasons, leaving 33 patients who were randomly assigned to the control group (CABG alone) and treatment group (CABG combined with aBMMNCs transplantation) in a 1:1 ratio (Figure). The random table was generated by SPSS software version 13 (SPSS, Chicago, IL, USA). The patients' assignment was blind to the physicians who treated the patients postoperatively and the investigators who performed the examination and interpreted the results. Echocardiogram assessments were applied in all patients at 6 months' and 24 months' clinical follow-up by a single senior echocardiographer.

The primary endpoints of the study were the changes of LVEF, LVEDV, and LVESV from baseline to six-month

and 24-month follow-up, respectively. The secondary endpoints were the changes of III and IV NYHA classification, 6-minute walk distance and BNP from baseline to follow-up. MACES during the follow-up were also recorded and compared between the two groups.

Bone Marrow Cell Preparation and Administration

20 mL of blood was taken from each patient to obtain serum after anesthesia. The standard midline skin incision was made and 80 mL bone marrow was aspirated from the patient's sternum into preservative-free heparin (10 U/mL) and diluted with normal saline. The aBMMNCs were isolated by density centrifugation with Ficoll-Paque Plus (GE Medical), washed twice with saline, and resuspended in the 3 mL autologous serum for injection. The viability of aBMMNCs after processing was tested greater than 95% immediately before administration. CABG was routinely performed on cardiopulmonary bypass (CPB) with HTK solution cardioplegia. On completion of distal anastomoses of saphenous vein grafts, 3 mL aBMMNCs solution was injected into the peri-infarcted region in 10-15 sites, approximately 0.5 cm apart, with a 27 gauge insulin needle. After injection, the left internal mammary artery to the left anterior descending coronary artery anastomosis was completed and the procedure was finished as standard way.

Biochemical Assessment

Creatinine kinase-MB (CK-MB) and troponin T levels were measured in venous blood samples taken within 24h after surgery. Serum pro-BNP levels were measured in venous blood samples preoperatively, 6-month, and 24-month follow-up, respectively.

Echocardiography

All patients underwent DSE before surgery and standard echocardiography test (IE33 Ultrasound System, Philip's Ultrasound systems) through the study. Left ventricular segmental wall motion was qualitatively assessed at rest echocardiography and during DSE according to the 17-segment model of the American Society of Echocardiography, and was defined as one of four categories (normokinesis, hypokinesis, akinesis, dyskinesis). The segment categorized to akinesis or dyskinesis both at rest echocardiography and DSE was defined as transmural scar and was the target of aBMMNCs transplantation. The parameters such as LVEF, LVEDV, and LVESV were collected and analyzed.

6-min Walk Test

6-min walk tests were performed for each patient before surgery and during follow-up visits following the American Thoracic Society guidelines [ATS Statement 2002]. Distance walked in 6 minutes along a standard 30-m hallway was recorded.

24-h Holter Monitoring

24-hour Holter monitoring tests were completed before surgery and during six-month and two-year follow-ups. The incidence of ventricular tachycardia recorded during follow-up was used as a parameter to evaluate the safety of intramyocardia injection of aBMMNC.

Follow-Up

All patients were followed up by outpatient visit or telephone communication every month in the first six months. Then the follow-up was carried out every three months until the end of the study. The completion of follow-up was 100%. The MACES, including all-cause death, cardiogenic death, sudden cardiac death, recurrent myocardial infarction, re-revascularization, rehospitalization for heart failure, and stroke, were recorded. Rehospitalization for heart failure was defined as hospitalization with typical clinical findings of heart failure requiring the addition of medication for the treatment of heart failure.

Table 1. Patients' Baseline Characteristics

	Treatment Group (n = 17)	Control Group (n = 16)	*P*
Age, y, mean ± SD	65.6 ± 3.97	65.5 ± 5.6	.923
Female, n (%)	28 (54.9)	34 (55.7)	.929
Hypertension, n (%)	6 (11.8)	12 (19.7)	.308
Diabetes, n (%)	3 (5.9)	1 (3.6)	.329
Current smoker, n (%)	3 (17.6)	5 (31.3)	.438
Prior CI, n (%)	12 (23.5)	8 (13.1)	.152
Logistic EuroSCORE (%)	4.75 ± 3.71	3.43 ± 1.54	.192
NYHA classification	2.94 ± 0.506	3.05 ± 0.590	.306
Inferior or posterior MI, n (%)	5 (29.4)	7 (43.8)	NS
Anterior, lateral, apex MI, n (%)	12 (70.6)	9 (56.2)	NS
Preoperative medication			
Aspirin, n (%)	16 (94.2)	16 (100)	NS
Clopidogrel, n (%)	1 (0.8)	0	NS
β-blockers, n (%)	14 (82.4)	14 (87.5)	NS
ACE inhibitors, n (%)	6 (35.3)	5 (31.3)	NS
Statins, n (%)	17 (100)	16 (100)	NS
Diuretics, n (%)	9 (52.9)	8 (50.0)	NS
Number of diseased coronary vessels			
One	0	0	NS
Two	0	0	NS
Three, n (%)	17 (100)	16 (100)	NS

CI indicates cerebral infarction; MI, myocardial infarction; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; NS, not significant.

Table 2. Perioperative Data of aBMMNCs Intra-Myocardial Injection

	Treatment Group (n = 17)	Control Group (n = 16)	*P*
CPBT (min)	122.27 ± 16.92	110.84 ± 23.45	.117
ACT (min)	84.33 ± 14.81	71.8 ± 20.2	.049
Number of grafts	3.57 ± 0.62	3.63 ± 0.77	.806
Postoperative laboratory test			
Peak CK-MB	15.98 ± 9.42	13.38 ± 7.29	.384
Peak Troponin T	0.47 ± 0.26	0.51 ± 0.28	.673
Mortality and morbidity within 30 days			
Death	0	0	NS
New Q-wave MI	0	0	NS
New onset AF, n (%)	3 (17.5)	2 (12.5)	NS
Ventricular arrhythmia	0	0	NS
Myocardial infarction	0	0	NS
Renal failure	0	0	NS
Re-exploration for bleeding	0	0	NS
Stroke	0	0	NS
Mediastinitis	0	0	NS
Sternal dehiscence	0	0	NS

CPBT indicates cardiopulmonary bypass time; ACT, aortic cross-clamp time; NS, not significant; AF, atrial fibrillation; MI, myocardial infarction; CK-MB, creatinine kinase-MB.

Table 3. Left Ventricular Function and Dimension Assessed by Echocardiography

	Treatment Group (n = 17 at 6 months)	Control Group (n = 16 at 24 months)	*P* (n = 16)
LVEF (%)			
Baseline	34 (4.46)	34.75 (2.9)	.506
6 months	42.5 (6.60)	39.5 (4.70)	.144
24 months	42 (6.34)	40.44 (7.36)	.525
Change 1	8.17 (4.36)	4.71 (3.49)	.020
Change 2	7.44 (5.43)	5.69 (6.61)	.419
LVEDV (mL)			
Baseline	156 (17)	161 (35)	.612
6 months	133.7 (30.6)	138.2 (34.5)	.696
24 months	127.4 (36.8)	135 (28)	.521
Change 1	-22.1 (26.7)	-22.5 (42.9)	.976
Change 2	-28.1 (39.3)	-25.8 (22.7)	.856
LVESV (mL)			
Baseline	100.6 (14.8)	105.6 (23.7)	.472
6 months	83.6 (26.1)	84.9 (25.2)	.880
24 months	79.5 (25.5)	81.2 (21.6)	.842
Change 1	-17.0 (24)	-20.7 (28.7)	.690
Change 2	-8.2 (31.0)	-24.5 (22.7)	.100

Change 1 indicates change between baseline and 6 months; Change 2, change between baseline and 24 months; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

Statistical Analysis

Continuous variables are presented as mean ± SD, unless otherwise specified. Categorical variables were compared between the two groups using Pearson chi-square test or Fisher exact test. Continuous variables were compared using unpaired t test or t' test. The nonparametric Mann-Whitney U test was also used as an alternative test because the data are likely abnormal distribution and the sample size of the study is small. All tests were two-sided and $P < .05$ was considered statistically significant. Analyses were performed with SPSS version 13.0.

RESULTS

Baseline Characteristics

A total of 33 patients were included in the study. The preoperative characteristics were similar between the two groups (Table 1). In the treatment group, an average number of $98.5 \pm 48.3 \times 10^6$ aBMMNCs per patient was injected into the peri-infarcted myocardial area in each patient.

Perioperative Results

All patients underwent the operations without death and major complications such as MI, stroke, reexploration for bleeding, and renal failure. Moreover, no complication related to bone marrow aspiration was observed, including mediastinitis and sternal dehiscence. The incidence of atrial fibrillation and that of ventricular arrhythmias were similar postoperatively in the two groups during stay in the hospital. There was no significant difference in CPB time and graft number between the two groups, though the cross-clamping time in the treatment group was longer than that of the control group caused by the injection of aBMMNCs (Table 2). Biochemical test didn't show any significant difference in postoperative peak level of CK-MB and troponin T between the two groups (Table 2). All patients were discharged within 14 days postoperatively.

Effect of Global Left Ventricular Function by Echocardiography

Baseline echocardiographic data was similar between the two groups (Table 3). Overall, patients in the treatment group experienced a significant increase in LVEF at 6 months postoperatively compared with the control group (P = .020,

Table 4. Clinical Outcomes at 6 Months

Clinical parameters	Treatment Group (n = 17)	Control Group (n = 16)	*P*
NYHA class III-IV			
Before surgery	13	13	NS
6 months after surgery	2	1	NS
6-min walk test (m)			
Before surgery	438 (37)	445 (30)	.570
6 months after surgery	533 (76)	528 (63)	.834
Distance change	95 (50)	83 (52)	.504
BNP*			
Baseline	2700 (870, 4668)	1099 (613, 3262)	.313
6 months after surgery	672 (337.6, 2308.5)	595 (314.3, 1445)	.614
Changing value	-854 (-2842, -158.4)	-401.5 (-930.3, -199.7)	.235
MACES			
All cause death	0	0	NS
Cardiogenic death	0	0	NS
Sudden cardiac death	0	0	NS
Recurrent MI	0	0	NS
Re-revascularization	0	0	NS
Rehospitalization for heart failure	0	0	NS
Stroke	0	0	NS
24-h Holter monitoring			
Ventricular tachycardia	0	0	NS

*Values are median (quartile). NYHA indicates New York Heart Association; BNP, B-type natriuretic peptide; MACE, major adverse cardiac events; MI, myocardial infarction; NS, not significant.

Table 5. Clinical Outcomes at 24 Months

	Treatment Group (n = 17)	Control Group (n = 16)	*P*
NYHA class III-IV			
Before surgery	13 (76.5)	13 (81.3)	NS
24 months after surgery	4 (25)	5 (31.3)	NS
6-min walk test (m)			
Before surgery	438 (37)	445 (30)	.570
24 months after surgery	528 (66)	514 (73)	.593
Distance change	88 (46)	70 (62)	.354
BNP*			
Baseline	2700 (870, 4668)	1099 (613, 3262)	.313
24 months after surgery	684.5 (327, 1219.8)	654.5 (417.3, 1196.3)	.880
Changing value	-830.3 (-2756.3, -282)	-337 (-985, -207)	.243
MACES			
All cause death	1	0	NS
Cardiogenic death	1	0	NS
Sudden cardiac death	1	0	NS
Recurrent MI	0	0	NS
Re-revascularization	0	0	NS
Rehospitalization for heart failure	4	3	NS
Stroke	0	0	0
24-h Holter monitoring			
Ventricular tachycardia (%)	1 (5.9)	2 (12.5)	NS

*Values are median (quartile). NYHA indicates New York Heart Association; BNP, B-type natriuretic peptide; MI, myocardial infarction; NS, not significant. Change = postoperative value-baseline value.

n = 33) (Table 3). However, this improvement was not found at 24-month follow-up (P = .419, n = 32) (Table 3). There was no significant change in any time point postoperatively between the two groups regarding the other primary endpoints (LVEDV, LVESV).

Clinical Outcomes at 6-Month and 2-Year Follow-Up

33 patients completed the first follow-up (6 months postoperatively) while 1 patient in the treatment group suffered from sudden death 10 months postoperatively, leaving 32 patients with available data on the 24-month follow-up.

Tables 4 and 5 summarize the clinical outcomes during 6-month and 2-year follow-up. There was no significant difference in proportion of III and IV NYHA classification, change of walking distance within 6 minutes, change of BNP level, and rate of MACES between the two groups during the follow-up.

DISCUSSION

To the best of our knowledge, this study was the only one with follow-up time longer than 24 months regarding treatment of chronic ischemic heart failure with aBMMNC therapy combined with CABG. Compared with previous congeneric studies, the most important findings of the present study are: (1) intra-myocardial injection of aBMMNC transplantation on arrested heart during CABG is a safe procedure without increase of ventricular tachycardia during the 2-year follow-up; (2) The patients with chronic ischemic heart failure can benefit from aBMMNC transplantation in the short-term (6 months), demonstrated by improved global LVEF compared with the control group. However, this benefit was not found at 2-year follow-up as shown by the clinical and echocardiographic results.

Table 6. Major Clinical Trials of aBMMNCs Therapy for Chronic Ischemic Heart Failure*

Study (Author, year)	Sample size	Inclusion criteria	LVEF/LVEDV evaluation	Type of cells	Study design	Follow-up (months)	Outcome
Patel 2005	20	Ischemic heart failure, LVEF <40%, NYHA III-IV	Echocardiography	CD34+ BMMNC	RCT	6	Improvement of cardiac function
Mocini 2006	36	Recent MI (>4 weeks but <6 months); no evidence of myocardial viability in the infarct area (LVEF 46 ± 6%)	echocardiography	BMMNC	RCT	12	Safe and feasible, significant improvement in left ventricular function
Hendrikx 2006	20	History of MI, indication for CABG, akinetic LV area (LVEF, about 40%)	Cardiac MRI	BMMNC	RCT	4	Recovery of regional function but not global left ventricular function
Stamm 2007	43	History of MI (>2 weeks), indication for CABG, instinct area of akinetic left ventricular ejection (LVEF 38 ± 8)	Echocardiography	CD133+ BMMNC	RCT	6	Safe and feasible improvement in LVEF and myocardial perfusion
Ang 2008	63	Irreversible myocardial scar, History of MI (>6 weeks, LVEF 25 ± 8%)	Cardiac MRI	BMMNC	RCT	6	Safe and feasible No improvement in cardiac function
Zhao 2008	36	History of transmural old myocardial infarction with akinesis or dyskinesis of the left ventricle; multivessel disease with a reversible perfusion defect detected by SPECT, LVEF <40%	Echocardiography	BMMNC	RCT	6	Improvement in cardiac function and regional perfusion
Shengshou 2011	60	History of MI (>3 months), planned CABG for triple vessels disease, no evidence of surviving myocardium on SPECT, LVEF <30% on MRI	Cardiac MRI	BMMNC	RCT	6	Improvement in cardiac function
Nasseri 2014	60	Chronic ischemic heart disease and impaired LV function (LVEF <35%)	Cardiac MRI	CD133+	RCT	6	No effect on global LV function and clinical symptoms, some improvements in scar size and regional perfusion
Patila 2014	39	LVEF between 45% and 15%, NYHA Class II-IV heart failure symptoms	Cardiac MRI	BMMNC	RCT	12	No improvement in LV systolic function, or viability, despite reducing myocardial scar size

*[Donndorf 2011; Patila 2014; Nasseri 2014].
aBMMNCs indicates autologous bone marrow mononuclear cells; ACEI, angiotensin-converting enzyme inhibitor; ACT, aortic cross-clamp time; AF, atrial fibrillation; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CI, cerebral infarction; CK-MB, creatinine kinase-MB; CPBT, cardio-pulmonary bypass time; DSE, dobutamine stress echocardiography; MI, myocardial infarction; NYHA, New York Heart Association; NS, not significant; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MACES, major adverse cardiovascular events; RCT, randomized controlled study.

One of the major concerns of intra-myocardia injection of aBMMNC was the possibility of increasing incidence of ventricular tachycardia or fibrillation, the main reason of sudden cardiac death (SCD). In the past 20 years, the safety of aBMMNC intra-myocardia injection combined with CABG has been proved by a series of RCTs and observational studies listed in Table 6. However, all of the safety evaluations by these studies were based on the perioperative and short-term (less than 6-month) clinical results except two studies, which had 1-year follow-up. We carried out the same methodology as most of the previous studies with aBMMNC intra-myocardial injection around peri-infarcted area on arrested heart. Our results showed that there was no significant difference in incidence of sudden cardiac death or increase of ventricular tachycardia between the two groups during the 2-year follow-up.

So far, almost all clinical studies regarding aBMMNC transplantation have been focused on the setting of acute myocardial infarction and that of chronic ischemic heart failure. A variety of studies have demonstrated longstanding (up to 4 years and more) improvement of ventricular performance after using intracoronary aBMMNC injection for patients

with AMI, resulting in an increase in ejection fraction by 3% to 36% (mean 11.4%) and decreased infarct size by 1% to 60% (mean 34%) [Lunde 2006; Cao 2009; Erbs 2007; Lipinski 2007; Penicka 2007; Huikuri 2008; Kang 2008; Beitnes 2009; Zhang 2009]. However, for patients with chronic ischemic heart failure undergoing combined aBMMNC therapy and CABG, most of the studies only showed a short-term (less than 6-month) efficiency with the increase of global LVEF from 2.5% to 10.2% [Donndorf 2011]. Two randomized controlled trials that sustained 12-month follow-up showed different results. Mocini et al found that patients with aBMMNC transplantation had significant improvement in LVEF and wall motion score index evaluated by echocardiography [Mocini 2006]. However, Patila et al, using MRI and PET-CT, demonstrated that aBMMNC therapy combined with CABG failed to improve LV systolic function, or myocardial viability, despite reducing myocardial scar size [Patila 2014]. Similar to the previous studies, our study showed the aBMMNC group had a 4% increase of LVEF in six-month follow-up compared with the control group. However, this improvement was not found in 2-year follow-up. The exact mechanism is not clear regarding the different effect of aBMMNC treatment on recovery of heart function under the circumstances of AMI and OMI. The paracrine effect and intervention time of aBMMNC therapy may play critical roles for the results. A series of experimental studies have demonstrated that aBMMNC can express a bounty of cytokines to prevent cardiomyocyte apoptosis, promote angiogenesis, and recruit intrinsic endogenous stem cells for cell regeneration and fusion [Bittner 1999; Alvarez-Dolado 2003; Beohar 2010]. All these effects can translate to prevention of left ventricular remodeling and improvement of left ventricle function. Thus, when aBMMNC is transplanted at the AMI setting, the left ventricular remodeling is more likely to be prohibited in its early phase and the left ventricular systolic function obtains the opportunity to improve steadily in the long term. However, when aBMMNC is transplanted at OMI setting in which the left ventricular remodeling has already developed, the paracrine effect of aBMMNC is mainly acting on the transitional zone of OMI, resulting in a limited reduction of MI size and short-term improvement of global left ventricular function with the vanishment of paracrine effect with time.

The 5-year follow-up results of Repair-AMI showed that aBMMNC therapy could significantly reduce the incidence of long-term MACES for patients suffering from AMI [Assmus 2014]. Our study didn't find any significant difference of MACES at the 2-year follow-up between the two groups. The relatively smaller sample size and shorter follow-up time may lead to this result and a prospective, multicenter, and long-term follow-up study is warranted in the future.

Study Limitations

Several study limitations should be addressed here. First, sample size in the present study was small, so long-term large-scale clinical trials need to be performed to verify the generalizability of the present conclusion. Secondly, there was a lack of evaluation by MRI and PETCT on target area in this study, which should be completed in future studies. Since our study is focused on the long-term results and global cardiac function rather than the segmental change in the scar area, this defect didn't influence the conclusion that the present study drew.

Conclusion

In summary, we have shown that intra-myocardial injection of aBMMNC transplantation on arrested heart during CABG is a safe procedure based on a longer period observation. The patients with chronic ischemic heart failure can benefit from aBMMNC transplantation in the short-term (6 months), demonstrated by improved global LVEF compared with the control group. However, this additional benefit was not found at 2-year follow-up as shown by the clinical and echocardiographic results.

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