Efficacy and Safety of Intracoronary Autologous Bone Marrow-Derived Cell Transplantation in Patients With Acute Myocardial Infarction: Insights From Randomized Controlled Trials With 12 or More Months Follow-Up

Address for correspondence:
Junbo Ge, MD
Shanghai Institute of Cardiovascular
Diseases
Zhongshan Hospital, Fudan University
180 Fenglin Road,
Shanghai 200032, China
jbge@zs-hospital.sh.cn

Chunyu Zhang, MD; Aijun Sun, PhD; Shuning Zhang, MD; Kang Yao, MD; Chaoneng Wu, MD; Mingqiang Fu, MD; Keqiang Wang, MD; Yunzeng Zou, MD; Junbo Ge, MD

Shanghai Institute of Cardiovascular Diseases, (C. Zhang, Sun, S. Zhang, Yao, Wu, Fu, Wang, Zou, Ge), Zhongshan Hospital, Fudan University, Shanghai, China; Institute of Biomedical Science, (Zou, Ge), Fudan University, Shanghai, China

ABSTRACT

Background: Until now there was no systematic review concerning the chronic effects of intracoronary bone marrow-derived cell (BMC) transplantation in patients with acute myocardial infarction (MI).

Hypothesis: Improvement of cardiac function in patients with acute MI post BMC transplantation might last longer than 12 months.

Methods: We searched MEDLINE, EMBASE, and the Cochrane database through June 2009. Eligible studies were randomized controlled trials of intracoronary BMC transfer in acute MI patients with follow-up duration equal to or longer than 12 months.

Results: A total of 8 trials involving 725 participants were identified. Compared with controls, BMC transplantation significantly improved left ventricular ejection fraction (LVEF) by 4.37% (95% confidence interval [CI]: 2.66%–6.08%; $P < 0.00001$), reduced left ventricular end-diastolic volume (LVEDV) by 5.71 mL (95% CI: 2.03–9.40 mL; $P = 0.002$), left ventricular end-systolic volume (LVESV) by 8.94 mL (95% CI: 4.22–13.66 mL; $P = 0.0002$), and infarct size by 2.42% (95% CI: 1.33%–3.51%, $P < 0.00001$). Bone marrow-derived cell treatment also significantly reduced the risk of death (relative risk [RR]: 0.33, 95% CI: 0.13–0.89; $P = 0.03$), while the risk of reinfarction was similar between the 2 groups (RR: 0.62, 95% CI: 0.09–4.12; $P = 0.62$). Subgroup analysis showed that the BMC transplantation-induced LVEF increase was more significant in patients age < 55 and with cells transferred 6 or 7 days after MI.

Conclusion: Beneficial effects of intracoronary BMC transplantation could last more than 12 months in acute MI patients.

Introduction

Despite continuous therapeutic advancements, myocardial infarction (MI) remains a major cause of death worldwide. Unlike other organs, the heart has a limited ability to regenerate cardiomyocytes to repair injured tissue after an MI. Experimental studies indicated that bone marrow-derived cells (BMC) could differentiate to cardiomyocytes and an intramyocardium injection of BMC improved cardiac function after an acute MI.^{1,2} Recent clinical trials and meta-analyses also showed that intracoronary

autologous BMC transfer after acute MI modestly improved left ventricular ejection fraction (LVEF) and significantly reduced left ventricular end-systolic volume (LVESV) and infarct size after acute MI within 12 months post BMC transplantation.^{3–11} However, it remains controversial whether the short-term benefits of BMC transplantation could last for more than 12 months. The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration trial (BOOST) suggested that BMC therapy did not improve LVEF at 5-year follow-up,¹² while the Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction (BALANCE) study showed a long sustained benefit of BMC treatment.¹³ In this systematic review referring randomized controlled trials with 12 months or longer follow-up data, we analyzed the chronic efficacy of intracoronary autologous BMC in patients with acute MI.

Chunyu Zhang, MD and Aijun Sun, PhD contributed equally to this work.

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Methods

Inclusion Criteria

The included studies met the following criteria: (1) randomized controlled trials; (2) patients with acute MI, who received percutaneous coronary intervention (PCI); (3) autologous BMC were intracoronary transferred in the treatment group; (4) the control group did not receive BMC; (5) follow-up duration ≥ 12 months; and (6) reported efficacy endpoints (LVEF, LVESV, left ventricular end-diastolic volume [LVEDV] or infarct size) and/or safety endpoints (death or reinfarction).

Data Sources

We searched MEDLINE, EMBASE, and the Cochrane database for controlled trials investigating the efficacy and safety of intracoronary autologous BMC transfer for patients with acute MI and did follow-ups for at least 12 months. The search strategy is shown in Supporting Figure 1. We checked the reference lists of identified articles, previous meta-analysis, and original studies identified by the electronic search to find other potentially eligible studies.

Data Extraction

The primary end point was the change in LVEF from baseline to follow-up. Secondary efficacy end points were changes in LVESV, LVEDV, and infarct size. The safety end points were death or reinfarction. End points were analyzed from the longest available follow-up data. Study search, selection, abstraction, and appraisal were all performed by 2 independent reviewers, with divergences resolved with consensus.

Statistical Analysis

The meta-analysis was done in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines with Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).¹⁴ All analyses were based on the intention-to-treat principle. A random-effect model was used due to the difference of patients' age, BMC dosage, follow-up duration, and time to transplantation among included trials. Heterogeneity of treatment effect was diagnosed by the use of Cochrane's Q-test, and regarded as significant if $P \leq 0.1$ ¹⁵; and the effect on the variation of pooled treatment effects was calculated by use of I^2 . I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error. We regarded I^2 of $<25\%$, 25% to 50% , and $>50\%$ as low, moderate, and high heterogeneity, respectively.¹⁶ We calculated the results with weighted mean difference (WMD) and 95% confidence intervals (CI) for efficacy outcomes with inverse variance method and relative risk (RR) and 95% CI for safety outcomes with the Mantel-Haenszel method.

Publication bias was assessed by Begg's and Egger's test. A 2-sided P value <0.05 was considered to be statistically significant.

Results

Selected Studies and Characteristics

Of the 397 identified citations, 60 were potentially eligible for inclusion and 55 out of these 60 citations were excluded after detailed review. We also checked the references of identified citations and citations with follow-up duration less than 12 months. An additional 3 articles and 4 conference abstracts were found (Supporting Figure 2). In all, 8 trials (9 comparisons) with 725 participants were included in this meta-analysis.^{12,13,17–24} One trial was a 3-arm comparison with 20 patients in each arm.²² The 2 BMC groups compared the efficacy of low dose and high dose BMC infusion. Of the 725 individuals, 369 were randomized to the BMC group and 356 to the control group. The basic characteristics of the included trials are summarized in Table 1. Table 2 summarized the patients and procedural characteristics of included studies. The mean age ranged from 51 to 57. The dosage of BMC ranged from 1.0×10^7 to 2.46×10^9 . The follow-up duration ranged from 1 to 5 years. Time to BMC transfer from the onset of acute MI ranged from 1 to 7 days. The Jadad method was used to assess the quality of the included studies (Table 1).²⁵

Assessment of Efficacy and Safety of BMC Transfer

Compared with the controls, the BMC transfer significantly improved LVEF by 4.37% (95% CI: 2.66%–6.08%; $P < 0.00001$) (Figure 1). BMC infusion also reduced LVEDV (WMD: -5.71 mL, 95% CI: -9.40 to -2.03 mL; $P = 0.002$; Figure 2A), LVESV (WMD -8.94 mL (95% CI: -13.66 to -4.22 mL; $P = 0.0002$; Figure 2B), and infarct size (WMD -2.42% , 95% CI: -3.51% to -1.33% , $P < 0.00001$; Figure 2C). For the safety end points, BMC transplantation was associated with a significant reduction in death (RR: 0.33, 95% CI: 0.13–0.89; $P = 0.03$; Figure 3A), while did not affect the risk of reinfarction (RR: 0.62, 95% CI: 0.09–4.12; $P = 0.62$; Figure 3B). However, a substantial degree of heterogeneity was observed in LVEF ($I^2 = 92\%$), LVEDV ($I^2 = 80\%$), and LVESV ($I^2 = 93\%$).

Subgroup Analysis

Subgroup analysis was performed to define the efficacy of BMC transplantation on LVEF, LVEDV, and LVESV in patients of various ages (<55 years and ≥ 55 yrs), the administered BMC number (<108 cells and ≥ 108 cells), the time to BMC transfer from the onset of acute MI (within 5 d and 6–7 d), and follow-up duration (1–3 yrs and 4–5 yrs; Table 3). LVEF improvement post BMC transfer was more significant in patients age <55 years (pooled WMD: 5.69%, 95% CI: 3.78%–7.61%, $P < 0.0001$) than patients age ≥ 55 years (pooled WMD:

Table 1. Main Features of Included studies

Study ID	Published Year	Patients Enrolled	Method to Generate Treatment Allocation	Outcome Assessment Blinded	Follow-Up (yr/yr)	Imaging Modality for LVEF Assessment	Jadad Score ^a
ASTAMI ^{17,18}	2008	100	Yes	Yes	3.0	Cardiac MRI	3
BALANCE ¹³	2009	124	Unclear	Unclear	5.0	Left ventriculography	2
BOOST ^{12,20}	2006	60	Unclear	Yes	5.0	Cardiac MRI	3
Cao ¹⁹	2009	86	Yes	Yes	4.0	Echocardiography	4
Janssens ²¹	2006	67	Yes	Yes	1.0	Cardiac MRI	5
Meluzin ^{22, b}	2008	60	Unclear	Yes	1.0	SPECT	3
REPAIRE-AMI ²⁴	2007	204	Yes	Yes	2.0	—	5
Yao ²³	2009	24	Yes	Yes	1.0	Cardiac MRI	4

Abbreviations: ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction; BALANCE, Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction; BMC, bone marrow-derived cells; BOOST, Bone Marrow Transfer to Enhance ST-elevation Infarct Regeneration; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MRI, magnetic resonance imaging; NR, no report; REPAIRE-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; SPECT, photon emission computed tomography; y, year or years.

^a The maximum score possible was 5, according to the Jadad scale.

^b Meluzin included 20 patients in the control group, 20 patients in the low cell dose group (Meluzin LD), and 20 patients in the high cell dose group (Meluzin HD).

−0.15%, 95% CI: −2.72%–2.42%, $P = 0.91$) and in patients who received BMC 6 or 7 days after acute MI (WMD: 5.33%, 95% CI: 3.11%–7.55%, $P < 0.00001$) than in patients who received BMC within 1 to 5 days (WMD: 1.98%, 95% CI: −1.54%–5.50%, $P = 0.27$). It seemed that efficacy on LVEF was similar in patients receiving low BMC ($<10^8$, pooled WMD: 5.03, 95% CI: −0.19%–10.25%, $P = 0.06$)

or high MSCs ($>10^8$, pooled WMD: 3.76%, 95% CI: 1.78%–5.74%, $P = 0.0002$). Additionally, BMC treatment was associated with a trend toward higher LVEF with follow-up duration of at least 4 years (WMD: 5.21%, 95% CI: −0.26%–10.68%; $P = 0.06$). Subgroup analysis also indicated that reductions in LVEDV and LVESV were more significant in patients age <55 or cells

Table 2. Patients and Procedural Characteristics of Included Studies

Study ID	Mean Age (y)	Men (%)	BMC Arm	Control Arm	Mean Cell Number Administrated (10^7)	Days to BMC Transfer From the Onset of MI
ASTAMI ^{17,18}	57	84	BMC aspiration	Heparinized plasma	6.8	6.0
BALANCE ¹³	51	90	BMC aspiration	NR	6.1	7.0
BOOST ^{12,20}	56	70	BMC aspiration	Heparinized plasma	246	4.8
Cao ¹⁹	51	94	BMC aspiration	Saline	50	7.0
Janssens ²¹	57	82	BMC aspiration	Saline and 5% autologous serum	30.4	1.0
Meluzin ²²	54	92	BMC aspiration	Cell suspension media	5.5	6.85
REPAIRE-AMI ²⁴	56	82	BMC aspiration	X-vivo media and 20% autologous serum	23.6	4.4
Yao ²³	52	85	BMC aspiration	Heparinized saline	19	4.3

Abbreviations: ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction; BALANCE, Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction; BMC, bone marrow-derived cells; BOOST, Bone Marrow Transfer to Enhance ST-elevation Infarct Regeneration; MI, myocardial infarction; NR, no report; REPAIRE-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; y, year or years.

Figure 1. Forest plot of WMD in LVEF in the BMC group compared to the control group. Abbreviations: BMC, bone marrow-derived cells; CI, confidence interval; IV, inverse variance; LVEF, left ventricular ejection fraction, SD, standard error; WMD, weighted mean difference.

transferred 6 or 7 days after acute MI compared to patients age ≥ 55 or cells transferred within 1 to 5 days after acute MI.

Sensitivity Analysis and Publication Bias Assessment

The study performed by Cao et al carried the greatest weight for all efficacy end points.¹⁹ A sensitivity analysis with or without this study showed that BMC transfer was still associated with significant effects on LVEF and LVESV and was associated with a trend toward significant effect on LVEDV and infarct size. This systematic review was based on a comprehensive search strategy. There was no publication bias as tested by both Begg's test and Egger's test (Begg's test: $P = 0.805$; Egger's test: $P = 0.491$).

Discussion

As far as we know, this is the first systematic review to evaluate the efficacy and safety of intracoronary autologous BMC transplantation in patients with acute MI receiving BMC transplantation for 12 months or more. Our results showed that intracoronary autologous BMC transfer significantly improved LVEF and significantly reduced the risk of death in BMC-treated acute MI patients compared with controls. For the second end point, BMC infusion significantly decreased LVEDV, LVESV, and infarct size. Subgroup analysis suggested that more significant improvement on LVEF, LVEDV, and LVESV were seen in patients aged < 55 and in patients receiving BMC transfer 6 or 7 days after acute MI. Of note, there

was a trend toward significant LVEF improvement with a follow-up duration of at least 4 years.

Several mechanisms might be responsible for the observed cardiac function improvement post BMC transplantation in patients with acute MI. Hematopoietic stem cells, as a subset of BMC, were the first adult stem cells reported to differentiate into cardiomyocytes when transplanted into infarcted mice hearts.¹ In human beings, BMC could differentiate into cardiomyocytes as was shown by the detection of Y-chromosome-positive cardiomyocytes in female donor hearts transplanted in male recipient hearts.²⁶ However, recent animal studies did not reveal the differentiation of BMC into cardiomyocytes.^{27–29} Therefore, the improved heart function observed in these studies might be driven by the paracrine mechanism. Secreted angiogenic factors and/or activation of pathways that promote cell survival might protect and rescue hypoxic myocardium, thereby limiting damage to tissue and improving heart function.³⁰

This systematic review shows that patients' age and timing of BMC transfer after acute MI were important determinants for LVEF improvement post BMC transplantation. In the first instance, more significant improvement of LVEF was seen in patients younger than 55 which might be related to the reduced homing capacity of BMC derived from elderly patients. Experimental study showed that treatment with BMC from young, but not from aged mice, significantly increased local blood flow in ischemic tissue in mice with limb ischemia.³¹ Moreover, transplantation of BMC from aged rats did not improve heart function after MI.³² Subgroup analysis based on the study by Cao et al

Figure 2. (A) Forest plot of WMD in LVEDV in the BMC group compared to the control group. (B) Forest plot of WMD in LVESV in the BMC group compared to the control group. (C) Forest plot of WMD in infarct size in the BMC group compared to the control group. Abbreviations: BMC, bone marrow-derived cells; CI, confidence interval; IV, inverse variance; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SD, standard error; WMD, weighted mean difference.

Figure 3. (A) Forest plot of RR for death in the BMC group compared to the control group. (B) Forest plot of RR for reinfarction in the BMC group compared to the control group. Abbreviations: BMC, bone marrow-derived cells; CI, confidence interval; IV, inverse variance; RR, relative risk; SD, standard error.

also suggested that younger patients might benefit more from BMC infusion than older patients.¹⁹ In the second instance, more significant LVEF improvement was observed when BMC were administered 6 or 7 days after acute MI compared to 5 days after acute MI. A more favorable niche of transplanted BMC at 6 or 7 days following acute MI, may contribute to the superior effects of BMC transferred during this time window. It is known that the infarct-related inflammatory process is strongest within 5 days post acute MI.³³ Moreover, vascular endothelial growth factor reached the highest concentrations at 7 days after MI.³⁴ These might facilitate the engrafted cells' homing, survival, and differentiation into adult cell types in the heart, then transformed into the observed beneficial effect on LVEF. So far, the effects of more delayed BMC transfer on LVEF

in patients with acute MI remains unknown. A randomized trial in patients with chronic MI showed that LVEF increased by 15% at 3 months post intracoronary BMC therapy, whereas LVEF reduced 1.0% at the same period in control patients.³⁵ Moreover, this benefit can be sustained for 2.5 years after MI.³⁶

One or more years after BMC transfer, significantly reduced LVEDV, LVESV, and infarct size were evidenced in treated patients, which suggested that BMC might attenuate left ventricular remodeling after acute MI. Previous studies indicated that postinfarction ventricular remodeling may aggravate the development of adverse cardiac events, such as ventricular arrhythmias, heart failure, and subsequent death.^{37,38} Thus, attenuated left ventricular remodeling might contribute to the reduced risk of death in the BMC group.

Table 3. Subgroup Analysis Assessing the Significance of BMC Dosage, Time to Cell Transfer From the Onset of Acute MI, and Follow-Up Duration on LVEF

Subgroup	LVEF		LVEDV		LVESV	
	WMD (95% CI, %)	P Value	WMD (95% CI, mL)	P Value	WMD (95% CI, mL)	P Value
Mean patients' age						
<55 years (155/159)	5.69 (3.78–7.61)	<0.00001	−7.65 (−11.87 to −3.44)	0.0004	−12.46 (−18.19 to −6.74)	<0.0001
≥55 years (113/114)	−0.15 (−2.72–2.42)	0.91	1.06 (−4.47–6.58)	0.71	−0.32 (−4.70–4.05)	0.88
BMC dosage						
<10 ⁸ cells (132/132)	5.03 (−0.19–10.25)	0.06	−8.18 (−14.36 to −2.01)	0.009	−15.25 (−21.75 to −8.74)	<0.00001
≥10 ⁸ cells (136/141)	3.76 (1.78–5.74)	0.0002	−4.74 (−9.41 to −0.08)	0.05	−6.43 (−11.91 to −0.96)	0.02
Time to transfer from the onset of MI						
1–5 days (75/76)	1.98 (−1.54–5.50)	0.27	−0.80 (−3.52–1.93)	0.56	−1.42 (−3.56–0.73)	0.20
6–7 days (193/197)	5.33 (3.11–7.55)	<0.00001	−9.19 (−14.29 to −4.10)	0.0004	−13.77 (−20.91 to −6.64)	0.0002
Follow-up duration						
1–3 years (135/136)	3.69 (1.64–5.73)	0.0004	−6.96 (−14.45–0.53)	0.07	−7.93 (−17.18–1.33)	0.09
4–5 years (133/137)	5.21 (−0.26–10.68)	0.06	−4.40 (−8.14 to −0.67)	0.02	−9.60 (−18.22 to −0.98)	0.03

Abbreviations: BMC, bone marrow-derived cells; CI, confidence interval; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; WMD, weighted mean difference.

There are several limitations in our present study. First, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI), the largest clinical trial with 204 participants, was not included in this analysis since the follow-up duration was less than 12 months.⁶ Second, as in other meta-analyses, the results should be interpreted with caution in that the individual studies varies greatly with respect to the characteristics of participants, duration of follow-up, time to cell transfer from the onset of acute MI, and number of BMC infused. Thirdly, due to the small number of trials included in this study, the results of the subgroup analyses were not solid enough.

In summary, this systematic review confirmed the beneficial effects of intracoronary BMC on cardiac function and ventricular remodeling as well as incidence of death in patients with acute MI at 1 or more years post BMC transplantation. Due to the limited sample size (725 participants), large randomized controlled trials are warranted to clarify the observed benefits. The ongoing REPAIR-AMI and Multicenter double blind trial of autologous bone marrow mononuclear cell transplantation through intracoronary injection post acute myocardium infarction (MiHeart/AMI) study will thus supply more surrogate evidence on the chronic effects of intracoronary BMC transfer in patients with acute MI.^{6,39}

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