Impact of Timing on Efficacy and Safety of Intracoronary Autologous Bone Marrow Stem Cells Transplantation in Acute Myocardial Infarction: A Pooled Subgroup Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Until now there were no clinical studies or systematic reviews to investigate the impact of timing on efficacy and safety of intracoronary bone marrow stem cell (BMSC) transfer in patients with acute myocardial infarction (AMI).

Hypothesis: Timing of BMSC administration might play an important role in the therapeutic response in AMI patients.

Methods: A systematic literature search of PubMed, MEDLINE, and Cochrane Evidence-Based Medicine (EBM) databases was made on randomized controlled trials with at least 3-month follow-up data for patients with AMI undergoing emergent percutaneous coronary intervention (PCI) and receiving intracoronary BMSC transfer thereafter.

Results: A total of 7 trials with 660 patients were available for analysis. Compared to baseline level, BMSC transfer at 4 to 7 days post-AMI significantly improved left ventricular ejection fraction (LVEF; 4.63% increase, 95% confidence interval [CI]: 1.00%–8.26%, $P = 0.01$), reduced left ventricular (LV) end-systolic dimensions (95% CI: -0.53 – -0.02 , $P = 0.03$), decreased the incidences of revascularization (odds ratio [OR]: 0.60, 95% CI: 0.37–0.97, $P = 0.04$), decreased the cumulative clinical events of death or recurrent myocardial infarction (OR: 0.32, 95% CI: 0.11–0.95, $P = 0.04$), and decreased culprit artery restenosis or ventricular arrhythmia (OR: 0.59, 95% CI: 0.36–0.96, $P = 0.03$) however these improvements did not reach statistical significance in emergent transfer trials (within 24 hour post-AMI). Compared with emergent transfer, intracoronary BMSC therapy at 4 to 7 days also significantly reduced the incidence of revascularization (P for interaction = 0.02).

Conclusions: BMSC transfer at 4 to 7 days post-AMI was superior to that within 24 hours in improving LVEF, decreasing LV end-systolic dimensions, and reducing the incidence of revascularization.

Introduction

Recent studies have shown optimism for the potential of bone marrow stem cells (BMSC) as a therapeutic option for acute myocardial infarction (AMI).¹ However, some critical issues remain unclear. One of these unsolved issues is the determination of the optimal timing for cell therapy post-AMI.^{2,3} There were no clinical studies investigating the efficacy and/or safety of BMSC therapy at various times after infarction. It is unknown whether the timing of intracoronary cell administration plays an important role in the therapeutic response in AMI patients

with reperfused myocardium. Therefore, we performed a pooled subgroup analysis of data from published, randomized, controlled trials to assess the impact of timing on efficacy and safety of intracoronary BMSC transfer after AMI.

Methods

Literature Search Strategy

We used the Cochrane Collaboration search strategy and searched PubMed, Ovid's MEDLINE, BIOSIS, EMBASE, and Cochrane Evidence-Based Medicine (EBM) Reviews databases from January 1990 through May 2007 to identify all eligible trials. Complex search strategies were formulated using the following medical subject headings (MeSH) terms and text words: bone marrow, stem cell, progenitor cells, cell transplantation, cell therapy, cardiac repair, and myocardial infarction. The search was supplemented by

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reviews of reference lists for all relevant studies. All relevant reports identified were included without language restriction.

Selection Criteria

Clinical trials investigating the effects of intracoronary autologous BMSC transfer for patients admitted within 24 hours after the onset of AMI were included and only clinical trials with both randomized controlled design and at least 3-month follow-up data on the efficacy/safety of the procedure were analyzed. Patients undergoing emergency percutaneous coronary intervention (PCI) in combination with standard medical treatment without BMSC transfer served as controls. Trials would be excluded if the route of cell transplantation was intravenous or intramyocardial injection, or the engrafted cells were circulating progenitor cells mobilized from bone marrow by granulocyte colony-stimulating factor.

Study Enrollment and Data Extraction

All the citations were reviewed by 2 investigators, in duplicate and independently, to identify eligible studies. The following information was extracted from each trial enrolled in the current study: basal characteristics of study, participant characteristics, intervention strategies, left ventricular ejection fraction (LVEF), left ventricular (LV) end-diastolic or end-systolic dimensions (volume, volume index, or diameter), and major adverse clinical events during follow-up. The eligible studies were graded with the 5-point Jadad quality scale.⁴

Statistical Analyses

Intergroup analyses of LV functional and anatomic parameters were based on the change from baseline data. Results of LVEF and LV dimensions were combined as weighted mean differences (WMD) and standardized mean difference (SMD) with 95% confidence intervals (CI) using random effect models, respectively. Pooled effect on the occurrence of adverse clinical endpoints was presented as odds ratio (OR) with 95% CI using a fixed-effects model. Alternatively, random-effects meta-analyses were performed when between-study variability existed. Heterogeneity was quantified using the I^2 statistic (inconsistency was defined as $I^2 > 50\%$). Sensitivity analyses excluding 1 study at each time were conducted to explore the heterogeneity. Statistical significance for hypothesis testing was set at the 0.05, 2-tailed level. We conducted planned subgroup analyses according to the timing of cell transplantation (within 24 h vs during 4–7 d) post-AMI and tested for treatment-subgroup interactions by performing logistic regression using Stata 8.0 software (Stata Corp, LP, College Station, TX). The pooled analyses were performed and forest plots were generated with RevMan v4.2 software (The Cochrane Collaboration, Copenhagen, Denmark).

Results

Selected Studies and Characteristics

The electronic database search identified 349 articles, among which 9 articles covering 7 randomized trials with 660 patients met the inclusion criteria.^{5–13} Table 1 summarized the basal characteristics and design features of individual studies. Intracoronary BMSC transfer was performed within 24 hours in 3 trials with 271 patients^{5,8,12} and at 4 to 7 days in 4 trials with 389 patients.^{6,7,9–11,13} The level of evidence for each article was graded with a score of 2 to 5 according to the Jadad quality score (Table 1).

Quantitative Assessment of Efficacy and Safety of BMSC Transfer at Different Times Post-AMI

Effect on LVEF and LV End-Systolic Dimensions: Overall, intracoronary BMSC transfer significantly improved LVEF and reduced LV end-systolic dimensions compared to the control patients (Figures 1 and 2). The pooled subgroup analyses demonstrated that BMSC transferred during 4 to 7 days post-AMI significantly improved LVEF and reduced LV end-systolic dimensions (LVEF: WMD = 4.63%, 95% CI: 1.00%–8.26%, $P = 0.01$, $I^2 = 72.2\%$; Figure 1; LV end-systolic dimensions: SMD = -0.28 , 95% CI: -0.53 – -0.02 ; $P = 0.03$, $I^2 = 0\%$; Figure 2) while cell delivery within 24 hours showed only a trend towards improvement in LVEF and reduction in end-systolic dimensions (LVEF: WMD = 3.27%, 95% CI: -1.95% – 8.49% , $P = 0.22$, $I^2 = 52.9\%$; Figure 1; LV end-systolic dimensions: SMD = -0.15 , 95% CI: -0.65 – -0.36 , $P = 0.57$; Figure 2). However, there were no significant differences between the 2 subgroups on LVEF and LV end-systolic dimensions at the end of follow-up (LVEF: WMD = 1.36%, $P = 0.67$; LV end-systolic dimensions: SMD = -0.13 , $P = 0.65$; Table 2).

Effect on LV End-Diastolic Dimensions: Compared with the controls, BMSC transfer had a neutral effect on LV end-diastolic dimensions after AMI (within 24 h: SMD = -0.79 , 95% CI: -2.44 – -0.84 , $P = 0.35$, $I^2 = 87.5\%$; during 4–7 days: SMD = -0.03 , 95% CI: -0.24 – -0.18 , $P = 0.77$, $I^2 = 0\%$; Figure 3).

Effect on the Incidence of Major Adverse Clinical Events: Odds ratio and their 95% CI for clinical safety endpoints were displayed in Figures 4 and 5. The safety outcomes of individual studies could be found in the supplemental data. The pooled statistics uniformly indicated that there were tendencies towards reduced incidences of the individual clinical adverse events and the cumulative endpoints of death, recurrence of myocardial infarction, revascularization, or rehospitalization for heart failure in the BMSC-treated group as compared to the control group (all OR < 1.0 ; Figure 4). Cell therapy at 4 to 7 days post-AMI yielded significant decrease in the incidences of revascularization (OR: 0.60, 95% CI: 0.37–0.97, $P = 0.04$), the cumulative clinical events of death or recurrent myocardial infarction

Table 1. Basal Characteristics of Clinical Trials Enrolled in the Analyses

Author (Ref)	Study Name	Year	Sample Size (n) ^a	Mean Age (y)	Women (%)	LVEF at Baseline	Study Items	Cell Type	Mean Time to PCI (hrs)	Mean Time to Cell Transfer (days after PCI)	Mean Follow-Up (Months)	Jadad Score
Janssens et al ⁵	ND	2006	33/34	56.9	18	47.69%	E & S	BMMNC	3.9 ^b	<1.0	4	5
Schachinger et al ⁶	REPAIR-AMI	2006	101/103	56.0	18	47.59%	E & S	BMMNC	7.3	4.3	4	5
Schachinger et al ⁷	REPAIR-AMI	2006	101/103	56.0	18	47.59%	E & S	BMMNC	7.3	4.3	12	5
Ge et al ⁸	TCT-STAMI	2006	10/10	58.5	10	56.00%	E	BMMNC	7.5	0.13	6	4
Wollert et al ⁹	BOOST	2004	32/33	56.3	30	50.54%	E & S	BMMNC	21.6	4.8	6	3
Meyer et al ¹⁰	BOOST	2006	32/33	56.3	30	50.54%	E & S	BMMNC	21.6	4.8	18	3
Lunde et al ¹¹	ASTAMI	2006	50/50	57.4	16	47.95%	E & S	BMMNC	3.7 ^b	6.0 ^b	6	3
Yao et al ¹²	ND	2006	92/92	58.2	11	47.40%	S	BMMNC	12.3	0.08	14	2
Suarez et al ¹³	ND	2007	10/10	53.5	25	37.50%	E	BMMNC	4.0	7.0	3	2

^aCell transfer group/control group.

^bMedian.

Abbreviations: ASTAMI, Autologous Stem Cell Transplantation in Acute Myocardial Infarction; BMMNC, bone marrow mononuclear cell; BOOST, Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration; E, efficacy; LVEF, left ventricular ejection fraction; ND, no data; PCI, percutaneous coronary intervention; REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; S, safety; TCT-STAMI, emergent transcatheter transplantation of stem cells for treatment of acute myocardial infarction.

Figure 1. The impact of timing of cell transfer on left ventricular ejection fraction. Abbreviations: BMSC, bone marrow stem cells; CI, confidence interval; n, sample size; PCI, percutaneous coronary intervention; SD, standard deviation; WMD, weighted mean difference.

Figure 2. The impact of timing of cell transfer on left ventricular end-systolic dimensions. Abbreviations: BMSC, bone marrow stem cells; CI, confidence interval; n, sample size; PCI, percutaneous coronary intervention; SD, standard deviation; SMD, standardized mean difference.

Figure 3. The impact of timing of cell transfer on left ventricular end-diastolic dimensions. Abbreviations: BMSC, bone marrow stem cells; CI, confidence interval; n, sample size; PCI, percutaneous coronary intervention; SMD, standardized mean difference; SD, standard deviation.

Table 2. Comparisons of Left Ventricular Parameters Between Cell Transplantation Within 24 Hours and Days 4 to 7

Subgroup Analyses	LVEF		LVESV		LVEDV	
	WMD (95% CI)	P Value	SMD (95% CI)	P Value	SMD (95% CI)	P Value
Within 24 hours	3.27 (−1.95, 8.49)	0.22	−0.15 (−0.65, 0.36)	0.57	−0.79 (−2.44, 0.86)	0.35
Days 4 to 7	4.63 (1.00, 8.26)	0.01	−0.28 (−0.53, −0.02)	0.03	−0.03 (−0.24, 0.18)	0.77
Intersubgroup comparison	1.36 (−4.99, 7.71)	0.67	−0.13 (−0.70, 0.44)	0.65	0.76 (−0.90, 2.42)	0.37

Intersubgroup comparison was performed by logistic regression.

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volumes; LVESV, left ventricular end-systolic volumes; SMD, standardized mean difference; WMD, weighted mean difference.

Figure 4. Odds ratio of BMSC infusion therapy with respect to individual and cumulative clinical endpoints. Five trials (eg, BOOST, REPAIR-AMI, ASTAMI, Janssens, and Yao) were included in the analysis. *Summary estimation by random-effect model due to the heterogeneity across the enrolled trials. Abbreviations: CI, confidence interval; HF, heart failure; MI, myocardial infarction; OR, odds ratio.

(OR: 0.32, 95% CI: 0.11–0.95, $P = 0.04$), culprit artery restenosis, or ventricular arrhythmia (OR: 0.59, 95% CI: 0.36–0.96, $P = 0.03$; Figure 5) vs the control group while these parameters were similar between the emergent cell transfer group and the control group (all $P > 0.05$). Moreover, the incidence of revascularization was significantly lower in the 4 to 7 days cell transfer group than that in the emergent cell transfer group (P for interaction = 0.02; Figure 5).

Sensitivity Analysis

Sensitivity analysis by excluding 1 study at a time confirmed the results from the overall analysis both in direction and in magnitude of statistical significance. After the exclusion of the study by Suarez et al¹³ and Ge et al⁸ from overall pooled analysis (or subgroup analysis) for LVEF and LV end-diastolic dimensions respectively, statistical heterogeneity across the trials enrolled in current study vanished ($I^2 = 30.8\%$, 0%, respectively).

Figure 5. The impact of timing of cell transfer on the incidences of individual and cumulative clinical events. Abbreviations: CI, confidence interval; HF, heart failure; MI, myocardial infarction; OR, odds ratio.

Publication Bias

Funnel plots were performed for all outcomes, and overall LVEF, LV end-systolic dimensions, LV end-diastolic dimensions, and cumulative clinical endpoints and these parameters were symmetrically displayed (plots not shown).

Discussion

As far as we know, this is the first systematic review to evaluate the impact of timing on the efficacy and safety of

intracoronary autologous BMSC transfer in patients with AMI. The main finding of the present study is that intracoronary BMSC transfer at 4 to 7 days is superior to that within 24 hours in terms of LVEF improvement, LV end-systolic dimension attenuation, and the reduction in the incidence of revascularization.

The reason for the superior effects of BMSC transfer at 4 to 7 days post-AMI compared to those of emergent BMSC transfer remains unclear and it might be associated with the more favorable biochemical myocardial microenvironment

Table 3. Major Adverse Clinical Events of the Individual Trials Enrolled in the Meta-Analyses

First Author (Reference)	Death				Revascularization				Recurrence of MI				Rehospitalization for HF			
	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N
Meyer et al ¹⁰	0/33	1/32	0.31 (0.01, 7.98)	5/33	4/32	1.25 (0.30, 5.15)	1/33	0/32	1/33	0/32	3.00 (0.12, 76.40)	1/33	3/32	0.30 (0.03, 3.07)		
Janssens et al ⁵	0/33	1/34	0.33 (0.01, 8.48)	16/33	10/34	2.26 (0.83, 6.17)	ND	ND	ND	ND	NE	ND	ND	NE		
Lunde et al ¹¹	ND	ND	NE	11/50	15/50	0.66 (0.27, 1.62)			1/50	0/50	3.06 (0.12, 76.95)	1/50	1/50	1.00 (0.06, 16.44)		
Schachinger et al ⁷	2/101	6/103	1.02 (0.14, 7.39)	22/101	47/103	0.50 (0.27, 0.92)	0/101	6/103	0/101	6/103	0.07 (0.00, 1.33)	0/101	3/103	0.14 (0.01, 2.37)		
Yao et al ¹²	0/92	0/92	NE	2/92	1/92	2.02 (0.18, 22.70)	2/92	0/92	2/92	0/92	5.11 (0.24, 107.93)	ND	ND	NE		
First Author (Reference)	In-Stent Thrombosis				In-Stent or Culprit Artery Restenosis				Ventricular Arrhythmia				Cancer			
	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N	OR (95% CI)	BMSC n/N	Control n/N
Meyer et al ¹⁰	0/33	0/32	NE	ND	ND	NE	1/33	2/32	1/33	2/32	0.47 (0.04, 5.44)	0/33	0/32	NE		
Janssens et al ⁵	0/33	1/34	0.33 (0.01, 8.48)	2/33	1/34	2.13 (0.18, 24.67)	0/33	3/34	0/33	3/34	0.13 (0.01, 2.71)	1/33	1/34	1.03 (0.06, 17.20)		
Lunde et al ¹¹	0/50	0/50	NE	10/50	9/50	1.14 (0.42, 3.10)	1/50	1/50	1/50	1/50	1.00 (0.36, 3.64)	1/50	0/50	3.06 (0.12, 76.95)		
Schachinger et al ⁷	1/101	3/103	0.33 (0.03, 3.26)	16/101	26/103	0.56 (0.28, 1.12)	5/101	5/103	5/101	5/103	1.02 (0.29, 1.50)	0/101	2/103	0.20 (0.01, 4.22)		
Yao et al ¹²	1/92	2/92	0.49 (0.04, 5.55)	7/92	7/92	1.00 (0.34, 2.97)	0/92	0/92	0/92	0/92	NE	0/92	0/92	NE		

A 95% CI crossing 1 indicates no statistical difference.

Abbreviations: BMSC, bone marrow stem cells; CI, confidence interval; HF, heart failure; MI, myocardial infarction; n/N, stem cell transfer group/control group; ND, no data; NE, not estimated; OR, odds ratio.

at 4 to 7 days compared with that within 24 hours post-AMI. Experimental studies showed that the excessive inflammatory process in the infarcted myocardium subdued at 1 week after AMI,¹⁴ and some cytokines such as vascular endothelial growth factor reached the highest concentrations at that moment.¹⁵ All these might facilitate engrafted cells homing, survival, and differentiation, which finally transformed to the observed beneficial effects of BMSC transfer at 4 to 7 days post-AMI on LV function and remodeling.

Previous studies also indicated that engrafted BMSC could differentiate into endothelial cells and thus promote angiogenesis, prevent cardiomyocyte apoptosis, and consequently contribute to the effect on LV remodeling.^{16–18} In this meta-analysis, the discordant change in LV end-diastolic and end-systolic dimensions post-BMSC transfer was observed. Because there was no difference in LV end-diastolic dimensions between the BMSC-treated group and the control group, a decrease in LV end-systolic dimensions may represent an improvement in LVEF.

Some authors raised significant concerns on the safety of BMSC transfer.^{19–21} In this pooled subgroup analyses, the incidence of revascularization was significantly lower in patients receiving BMSC transfer at 4 to 7 days compared with both the control group and those receiving emergent BMSC transfer, indicating the important impact of timing on safety and clinical outcomes. The potential mechanism is not well documented in previous studies. Recent studies suggested that BMSC infused into the coronary circulation at 4 to 7 days post-AMI reconstituted the damaged endothelium and promoted neovascularization,²² which increased coronary flow reserve in the infarct-related artery. The improved perfusion capacity might stimulate the endothelium to release nitric oxide, which exerted antiatherosclerotic functions and might counteract the process of restenosis development and atherosclerotic disease progression.^{7,23} On the basis of these findings, we speculate that the improvement in coronary blood flow reserve might be one of the mechanisms responsible for the observed reduction in revascularization procedures in patients receiving BMSC transfer at 4 to 7 days post-AMI.

Taken together, BMSC transfer at 4 to 7 days post-AMI was superior to that within 24 hours in improving LVEF, attenuating LV end-systolic dimensions, and reducing the incidence of revascularization. BMSC transfer during 4 to 7 days post-AMI might be safer and more feasible than that within 24 hours. Maintenance of statistical significance when only selecting randomized controlled trials and using random effect model lends support to the robustness of our analysis. In addition, larger randomized clinical trials are required to further validate the observations made in this pooled subgroup analysis of randomized controlled trials based on limited clinical trials with relatively small population sizes.

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