Stem Cells Therapy for Acute Myocardial Infarction: A Literature Review

CHIUNG-ZUAN CHIU1,2,3, KOU-GI SHYU1,3

Clinical outcomes of acute myocardial infarction (AMI) have significantly improved after the use of reperfusion therapy (thrombolysis, percutaneous coronary intervention, or coronary artery bypass grafting). However, congestive heart failure resulting from ventricular remodeling after AMI continues to be a major problem. Recent literatures review confirms that stem cells (either derived from bone marrow or peripheral blood) can be effectively and safely delivered into infarcted myocardium by intracoronary, intramyocardial, or combinational (intracoronary and intramyocardial) transfer. In meta-analysis of randomized controlled trials, stem cells transferred after AMI can improve left ventricular (LV) ejection fraction, decrease LV volume and diameter, and reduce infarct size. The major factor related to favorable outcomes is the early transfer of a sufficient amount of stem cells (within 7 days after AMI) and with at least $>10^8$ cells. Major adverse cardiovascular events and mortality rates remain unchanged as compared with the control group, which means that stem cells transfer is safe and does not increase further risk.

Key words: acute myocardial infarction, congestive heart failure, stem cell transfer

Introduction

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality in modern society and may subsequently develop into congestive heart failure (CHF) in some patients. Pharmacological therapies (aspirin, angiotensin converting enzyme inhibitors, beta-blockers, and thrombolytic agents) have been used successfully in treating AMI patients and increasing life expectancy. Primary angioplasty has also been shown to decrease early mortality of AMI by a half\textsuperscript{(1-3)}. However, heart tissue has a diminished ability to repair itself after AMI as compared with other tissues in the body and some patients may eventually develop CHF with left ventricular (LV) remodeling even under optimal medical and interventional therapy. Myocardial dysfunction after AMI may further impair the circulatory function of the cardiovascular system and reduce adequate perfusion to the vital organs, which further worsens the life expectancy and long-term prognosis in patients with AMI.

Alternative therapies for myocardial dysfunction after AMI such as the use of stem/progenitor cells have recently been studied to complement the inadequate effect of pharmacological agents and primary angioplasty\textsuperscript{(4-12)}. The rationale for cell therapy in AMI is trying to use these cells to replace or repair the injured myocardium that has no ability to regenerate.

Phase I of the clinical trials using stem cells in

Received: August 20, 2009   Accepted for publication: October 21, 2009
From the 1Division of Cardiology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital
2 Fu Jen Catholic University School of Medicine
3Graduate Institute of Clinical Medicine, Taipei Medical University
Address reprint requests and correspondence: Dr. Kou-Gi Shyu
Division of Cardiology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital
95 Wenchuan Road, Shihlin District, Taipei 11101, Taiwan (R.O.C.)
Tel: (02)28332211 ext 2084   Fax: (02)28123397
E-mail: juice243@hotmail.com
AMI started in 2002 and indicated an improvement in clinical outcomes and cardiac function\(^{4-9,11-12}\). In addition, stem cells transfer in AMI was thought to be safe\(^{6,10}\). Preclinical experiments also indicated that stem cells transfer may contribute to the revascularization of ischemic infarcted myocardium\(^{10}\). The real mechanisms of stem cell induced revascularization in AMI remain unclear but may be multifactorial. The possible mechanisms involved include transdifferentiation into cardiomyocytes, cell fusion, paracrine effects, and neovascularization\(^{10,14-17}\). In order to understand the effect, benefit, and risk of stem cells therapy for AMI, randomized controlled trials (RCTs) were performed over the last past 5 years\(^{18-22}\). However, the patients enrolled in most studies were limited with only ten to less than one hundred cases taking part. So meta-analysis for all RCTs trials is necessary in order to obtain a more conclusive understanding of stem cells therapy in AMI.

### Inclusion and exclusion criteria

The clinical trials were eligible for inclusion if (1) Patients with ST elevation AMI had been reperfused successfully by means of primary coronary intervention; (2) they were RCTs; (3) The intervention consisted of any autologous bone marrow-derived stem cells (BMSCs) freshly isolated without restriction by dose or administration route; (4) Co-interventions with granulocyte colony-stimulating factor (G-CSF) were equally applied to each treatment arm; (5) Myocardial viability in the AMI region had been preserved with mild to moderate depressed LV function (LV ejection fraction: 30-50%).

Trials were excluded if any of the following factors were present: (1) BMSCs were cultured in vitro for longer than 24 hours prior to infusion, as this may have resulted in enrichment of a particular progenitor cell population; (2) Cardiac surgery had been previously performed; (3) Small areas of infarction existed; (4) There was a prior history of myocardial infarction; (5) Regional wall motional abnormality was present outside the area in the index of AMI; (6) Ventricular thrombus; (7) Severe valvular heart disease; (8) Severe liver, lung, renal, or hematopoietic disease; (9) Severe anemia (hemoglobin level less than 9.0mg/dl; (10) New York Heart Association (NYHA) functional class IV; (11) Post infarction angina pectoris; (12) Participation in other ongoing AMI trials; (13) Severe LV dysfunction (LV ejection fraction < 30%).

### Route of stem cells delivery

Two major routes of delivery were used in previous trials\(^{18-22}\). One was via intracoronary delivery and the other by the intramyocardial route. Intracoronary delivery is easy to perform without additional cost and can be achieved within 15 minutes. Procedural risks may occur during occlusion of the artery due to cell clots, flow cessation, or arterial stenosis. The earliest time point for intracoronary application is within hours after AMI. Intramyocardial delivery was achieved by target intramural transfer of stem cells in the ischemic areas. Three dimensional electromagnetic guidance NOGA system (Cordis Copr., Miami Lakes, FL) with diagnostic and injection catheter was used. The delivery time, however, is longer (>45 minutes) and the cost is considerably higher. The notable procedural risk is possible myocardial perforation. The optimal time for intramyocardial delivery is after the subsidence of AMI-related inflammation (at least 14 days after AMI). Recent trials\(^{19}\) also attempted to use combinational (intracoronary and intramyocardial) methods to identify if better efficacy of delivery can achieve better clinical outcomes after stem cell therapy.

### Bone marrow-derived stem cells (BMSCs)

Stem cells harvested either from the bone
marrow or from peripheral blood after bone marrow mobilization by G-CSF belong to bone marrow-derived stem cells (BSMCs).

**Timing of BMSCs delivery**

In the case of intracoronary BMSCs delivery, early delivery is performed within 7 days of AMI. In one RCT\(^{(18)}\), bone marrow harvest was performed within 24 hours of AMI, and stem cell delivery was performed as early as 4-6 hours after bone marrow harvest. Other RCTs\(^{(19-22)}\) selected late BMSCs delivery weeks or even months after AMI. In cases of intramyocardial delivery, several previous studies indicated that the homing of the transplanted cells is more effective after acute inflammation of the infarcted myocardial tissue has subsided (14 days after AMI) but the outcome is jeopardized by myocardial stunning (mainly 7-21 days after AMI but can be up to 3 months)\(^{(23-27)}\). Early intramyocardial delivery may increase the risk of myocardial perforation and electrical instability, so its earliest delivery time is 3-6 weeks after AMI. Several studies even delayed the intramyocardial delivery to 3-4 months after AMI.

**Number of BMSCs delivery**

The volume and number of cells delivered by the intracoronary route are unlimited. However, retention of the delivered cells to avoid washout is necessary for the cells migration through the arterial wall. A previous trial indicated\(^{(28)}\) that a requirement of at least 5×10^7/kg implanted cells is needed for cardiac mononuclear cell therapy to be effective. In most RCTs\(^{(18-22)}\), the average number of cells delivered in stem cell therapy ranged from 10^6 to 10^9. In intramyocardial delivery, the volume of delivered cell suspension is usually less than 4.0 ml and the number of cells delivered is up to 5×10^9.

**Image Studies**

Several different image studies, including echocardiography, cardiac MRI, single-photon emission CT (SPECT), or quantitative left ventricular (LV) angiography, were used in RCTs\(^{(18-22,29)}\). Left ventricular ejection fraction (LVEF), LV diameter, and LV volume before and after stem cell therapy were evaluated by these methods.

Echocardiography is the most commonly used tool to evaluate LVEF and size. Cardiac SPECT imaging is the most available tool for the measurement of infarct size. Contrast LV and radionuclide angiography have major error rates with a wide variation being noted between methods, probably owing to hibernating or stunned myocardium\(^{(20-24)}\). Cardiac MRI is currently recommended for the measurement of infarct size and LV function\(^{(18-22)}\). In cases of intramyocardial delivery, myocardial viability can be defined by NOGA mapping\(^{(19)}\) expressed as voltage values in the intramyocardially treated areas within the groups. In recent trials, myocardial velocity imaging (MVI) or velocity-derived strain rate imaging was used in patients with ST elevation. Myocardial infarction (MI) to measure regional myocardial deformation of LV by wall motion score index (WMSI)\(^{(18)}\). MVI can further evaluate the improvement of LVEF in different segments (infarct, border, and remote) of LV.

**Clinical Outcomes**

1. **Primary end points:**

The primary end points may include changes in global LVEF/diameter (functional end point) and infarct size (morphological end point) measured by echocardiography, SPECT, and cardiac MRI before and after BSMC therapy.
2. Secondary end points

The secondary end points were the feasibility of different delivery modes, determined by: the rates of acute and subacute complications and safety, expressed by the frequency of long-term major adverse cardiac events (MACE) during follow-up; changes in LV wall motion score index measured by image studies described earlier; improvement of the myocardial unipolar voltage as a parameter of myocardial viability with segmental wall motion, expressed by linear local shortening on NOGA mapping; changes in LV end-diastolic and end-systolic volumes; and improvement of clinical symptoms expressed by NYHA and Canadian Cardiovascular Society scores.

3. Major adverse cardiac events (MACE)

The MACE may include ventricular arrhythmia, rehospitalization for heart failure, and a composite of other cardiovascular events (cardiac death, recurrent myocardial infarction, infarct-vessel revascularization, and stroke).

Meta-analysis indicated BMSC transfer improves global LVEF, decreases LV diameter and volume, and reduces infarct size

Several review articles did meta-analysis for previous RCTs and indicated better outcomes in primary end points\(^ {18-22}\). Zhang et al.\(^ {20}\) reviewed 6 trials with 525 patients. Meta-analysis showed the mean increase in LVEF from baseline was 7.05% in the BMSC Group (\(P=0.01\)), but only 2.46% in the control group (\(P=0.02\)), and the effect on the absolute change in LVEF was an increase of 4.77% compared with the control (95% confidence interval [CI] 1.42% to 8.12%; \(P=0.005\)). A similar effect on LV end-diastolic diameters was demonstrated in an inter-group comparison (\(P=0.041\)). Martin-Rendon el al.\(^ {22}\) reviewed 13 trials with a total of 811 participants. Overall, stem cells therapy improved LVEF by 2.99% (95% CI, 1.26-4.72%, \(P=0.0007\)), significantly reduced LV end-systolic volume by 4.74 mL (95% CI, -7.84 to -1.64 mL, \(P=0.003\)), and myocardial lesion area by 3.51% (95% CI, -5.91 to -1.11%, \(P=0.004\)) compared with controls. Kang et al.\(^ {18}\) reviewed 16 RCTs with 517 patients and had similar results. Compared with the control groups, BSMC therapy produced a slight improvement of the follow-up LVEF (2.53%, 95% CI: 0.67 to 4.39, \(P=0.008\)) between 3 and 6 months. Similarly, BSMC therapy also significantly improved the LVEF change from baseline to follow-up (2.88%, 95% CI: 1.69 to 4.08, \(P=0.000\)) compared with the control groups. Gyöngyösi et al.\(^ {19}\) used a combined delivery approach of BMSC (intracoronary and intramyocardial) with early (3 to 6 weeks) and late (3 to 4 months) treatments after AMI to evaluate the effect of stem cells therapy. Results showed a moderate but significant improvement in infarct size and LVEF. In the 60 patients treated, the mean changes in infarct size at 3 months were -3.5±5.1% (95% CI -5.5% to -1.5%, \(P=0.001\)) in the early group and -3.9±5.6% (95% CI -6.1% to -1.6%, \(P=0.002\)) in the late group, and changes in ejection fraction were 3.5±5.6% (95% CI 1.3% to 5.6%, \(P=0.003\)) and 3.4±7.0% (95% CI 0.7% to 6.1%, \(P=0.017\)) respectively. 9 to 12 months after AMI, ejection fraction remained significantly higher than the baseline in both groups.

Early BSMC transfer with enough cells delivered is the key point for successful therapy

In different RCTs\(^ {18-22}\), BSMC deliveries were performed at different times after AMI. Herbots et al.\(^ {18}\) delivered BSMC 4-6 hours after bone marrow harvest, which was about one day after primary percutaneous coronary intervention (PCI). In 67 ST segment elevation myocardial infarction (STEMI) patients treated with intracoronary delivery,
LV regional myocardial deformation improved significantly more in the infarct segments of BMPC patients after 4 months. Other trials used either early (7 days after AMI) or late (weeks to months after AMI) BSMC transfer in treating AMI patients. In meta-analysis\(^{(19-22)}\), both early and late BSMC transfer had better primary outcomes as compared with control groups. However, early delivery seems to have better outcomes than late delivery in most RCTs\(^{(18-22)}\). The number of cells delivered is another important factor for successful therapy. An average of \(10^6\) to \(10^9\) cells were delivered in most RCTs\(^{(18-22)}\). One study indicated that the delivery of a sufficient number of cells (at least > \(10^8\)) delivered is the key to successful stem cells therapy\(^{(19)}\). Another review article also indicated that early therapy (within 7 days of AMI) with adequate cells (>\(10^8\)) delivered may achieve the best results\(^{(18-22,28)}\).

**Infarct area and border zone of infarct get most benefit from stem cells therapy**

In the study of Herbots et al.\(^{(18)}\), cardiac MRI was used to group different segments of myocardium after AMI; infarct, border, and remote areas. Then regional wall motion deformation was measured by velocity-derived strain rate imaging. Results showed that BMSC therapy improved LV regional myocardial deformation most in infarct areas and partially in border segments of AMI.

**No evident difference in MACE between stem cells therapy and control groups**

Some RCTs and review articles collected the MACE after BMSC therapy\(^{(16-22)}\). Although primary outcomes improved after stem cells therapy, MACE did not decrease significantly when compared with control groups. It indicated that the morbidity (ventricular arrhythmia, rehospitalization for heart failure, revascularization for infarct vessel) and mortality rates did not change after BMSC therapy

**The safety of stem cells therapy is acceptable in previous RCTs**

Another major concern is the feasibility and safety of BMSC therapy. In meta-analysis of different RCTs\(^{(18-22)}\), stem cell therapy by means of different routes or approach did not significantly increase the risk during or after therapy. However, probable complications of intracoronary or intramyocardial delivery should be kept in mind and be prevented.

**Mechanisms of action of stem cells**

The exact mechanism of stem cells and how they act on infarct myocardium remains unclear but may be related to the activation of resident progenitor cells by a paracrine mechanism. Angiogenesis, transdifferentiation into cardiomyocyte, cell fusion, and immune modulation are other possible mechanisms\(^{(10,14-17)}\). These effects may persist for days to months after cells transfer. Rota et al.\(^{(17)}\) have demonstrated in mice that adult c-kit+ BMSC implanted in the infarcted myocardium lose their hemopoietic phenotype over time and acquire the cardiogenic and endothelial lineages, forming functional cardiomyocytes and vascular structures. So cardiac niche may be crucial in modulating BSMC engraftment and fate. In addition, the production of cytokines (vascular endothelial growth factors (VEGF)) or specific progenitor cell subsets enrich the endothelial, mesenchymal, or monocytic progenitors in the BSMC fraction and may contribute to revascularization, reduce inflammation, or affect ventricular remodeling\(^{(30,31)}\).

**Difference in route of delivery**

Intracoronary and intramyocardial delivery are two major routes of stem cell transfer. Intracoronary delivery is the most frequently used method in RCTs. Intramyocardial delivery should be used later after AMI under the assistance of the NOGA
system. The efficiency of intramyocardial delivery may be better but the risk of myocardial perforation should be of concern. One study (32) also used intravenous delivery of progenitor cells and had a relatively good outcome.

**Difference in timing of delivery**

Both early (within 7 days of AMI) and late delivery can achieve improvement in primary outcomes in most RCTs and meta-analysis (18-22). However, systemic and subgroup analysis both revealed better primary outcomes in early delivery groups. Herbots et al. (18) even delivered BMSC as early as 4-6 hours after bone marrow harvest. The significant improvement in LVEF within 7 days after AMI and BSMB infusion may be explained by an increase in cytokines such as VEGF, hepatocyte growth factor (HGF), and G-CSF in plasma during the first week after AMI (33). It has been reported previously that VEGF presents two peaks of release during AMI, the first one in the acute phase (24-48 hours) and the second in the subacute phase (7 days) (30-31, 33). Other trials, including REPAIR-AMI (34-35), also indicated that late delivery (> 7days) achieved great improvement in LVEF. In cases of intramyocardial delivery, late delivery (at least > 3 weeks after AMI) is suggested because of the need to wait for the subsidence of myocardial inflammation. The effect of late delivery on improvement of LVEF could be detected from 3-4 weeks to even 3-4 months after AMI in previous studies (7-8).

**Difference in number of cells delivered**

The minimal number of cells needed to achieve significant improvement in LVEF remains unclear. However, systemic studies indicate that the number of cells delivered has a positive correlation with the improvement in LVEF. Subgroup analysis in meta-analysis revealed BMSC cells delivered more than $10^8$ ($10^9$ to $10^{10}$) may achieve significant improvement in LVEF compared with lower cell numbers delivered via the intracoronary route. In cases of intramyocardial delivery, a lower number of cells (up to $5 \times 10^8$) is necessary due to limited space and the need for better efficiency of cells transfer.

**Different efficacy of various cell types used**

A majority of RCTs and trials enrolled for meta-analysis made use of unfractionated bone marrow mononuclear cells, which increased LVEF by an average of 3 to 8% after BMSC therapy (19-22, 36-37). Chen et al. (38) used bone marrow mesenchymal stem cells, which might in some way contribute to discrepancies in the results of these studies. Bone marrow mesenchymal stem cells transplantation was more beneficial to LV function after AMI than bone marrow mononuclear cell transplantation, which was proved by Chen et al. and other clinical studies (39-43, 45). In the study of Chen et al, it is suggested that bone marrow mesenchymal stem cells transplantation may increase LVEF by up to 18%, which is much more effective than traditional mononuclear stem cell transplantation. Chen et al. also found that bone marrow-derived progenitor cells resulted in moderate improvement of LVEF in their trial. In fact, differences in BMSC processing methods have been reported to affect cell viability and expression of surface receptors or adhesion molecules (e.g. CXCR4 or connexin 43) that play a crucial role in BMSC homing to and retention in the regions of damaged tissue (45).

**Safety and MACE**

Another major concern about stem cell therapy is the safety and MACE rates compared with control groups. Different RCTs (18-22, 44) recorded MACE rates, mortality, and morbidity to evaluate clinical outcomes after BMSC therapy. In meta-analysis, mortality, morbidity (re-
infarction, arrhythmia, restenosis, re-admission, and revascularization), and adverse events did not reveal significant differences between stem cell therapy and control groups. These results mean: (1) Stem cells therapy does not increase adverse events and mortality, so safety may be the same as for control groups; (2) Stem cells therapy improves primary outcomes of patients (e.g. LVEF) but it does not further decrease mortality and cardiac morbidity of patients receiving BSMC transfer.

**Long-term efficacy**

Stem cells therapy results in benefits in improving LVEF, reducing infarct size and LV diameter/volume after follow-up for 3 months. However, the long-term efficacy of BMSC therapy remains unclear. The final 1-year results for TOPCARE-AMI trial\(^6\) confirmed a sustained improvement in LV function. But in BOOST trial\(^2\) the beneficial change in LVEF, documented 6 months later, had become non-significant 18 months later compared with the control. Therefore, further studies may focus on the long-term result of BMSC therapy and if repeated infusions yield additional benefits and risks.

**Conclusion**

Stem cell therapy for patients with AMI may complement the insufficiency of reperfusion therapy. In meta-analysis for RCTs, BMSC therapy may improve LVEF, reduce infarct size, and decrease LV diameter through different delivery routes and methods days to months after AMI. These benefits may persist at least 3 to 6 months after therapy, but the long-term effect (> 1 year) should be investigated in the future. Early transfer (< 7 days after AMI) and a sufficient number of cells delivered (> 10^6) has been proven to have a positive correlation to the improvement in LVEF in subgroup analysis. The risk, MACE rates, morbidity, and mortality of stem cell therapy did not have a significant difference with control groups.

**References**

15. Gyöngyösi M, Lang I, Dettke M, et al. Combined delivery approach of bone marrow mononuclear stem cells early and late after myocardial infarction: the MYSTAR prospec-


幹細胞治療於急性心肌梗塞之文獻回顧

邱俊仁\textsuperscript{1,2,3} 徐國基\textsuperscript{1,3}

急性心肌梗塞之治療於引用緊急再灌流治療(reperfusion therapy)後已有長足進步。但心肌梗塞後合併心臟衰竭為影響日後病患之一大難題。幹細胞治療用於心肌梗塞後病患經近年來綜合研究分析認為可取代及彌補傳統治療之不足，而達到改善左心室輸出功率，減少左心室直徑，及減少梗塞面積之功能。一般認為，早期(心肌梗塞7天內)及足量(大於$10^8$細胞)之幹細胞治療可達到最大功效。而幹細胞治療一般認為具有足夠的安全性，因為研究顯示主要心血管副作用及死亡率與對照組相比並無明顯差別。

關鍵詞：急性心肌梗塞，心臟衰竭，幹細胞治療

\textsuperscript{1}新光吳火獅紀念醫院心臟內科  \textsuperscript{2}天主教輔仁大學醫學系  \textsuperscript{3}台北醫學大學臨床醫學研究所

通訊及抄印本索取：徐國基醫師  111台北市士林區文昌路95號

新光吳火獅紀念醫院心臟內科

電話：(02)28332211轉2084  傳真：(02)28123397

E-mail: juice243@hotmail.com