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Review Article

Different time duration efficiency and feasibility of bone marrow-derived cells in ST-elevation myocardial infarction: a meta-analysis

Zemin Xu, Xiangling Zhang, Ping Zheng, Zhikuan Luo

Department of Intensive Care Unit, Tianjin Fourth Central Hospital, Tianjin 300140, China

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Abstract: Background: Bone marrow-derived cell (BMC) therapy has become a potential strategy to treat patients with acute myocardial infarction (AMI). However, the therapeutic efficacy of this modality remains controversial. The present meta-analysis was preformed to investigate the safety and efficiency of BMC therapy in different time durations. Methods: We conducted a systematic search of PubMed and EMBASE databases up to August 2017. After careful evaluation, twenty-nine studies involving 3,099 patients were included in this analysis. Mean changes of left ventricular ejection fraction (LVEF) in each time points were our outcomes of interest. All the data were combined using a random effects model. Subgroup analysis based on imaging modalities was conducted to explore the source of heterogeneity. Results: At 1 week, 1 month, 3 months, and 4 months, cell therapy patients did not show a significant difference in LVEF compared with the control group. Significant improvement on LVEF in cell therapy patients emerged at 6 months. The increase of LVEF became more profound at 12 months follow-up in BMC group compared with controls, and the beneficial effect sustained to 18-60 months. Subgroup analysis revealed that different measuring modalities might be one of the sources of heterogeneity among studies. Conclusions: BMC therapy seems to be safe and can provide statistically and clinically benefits on cardiac function. Further studies should be conducted to evaluate the therapeutic efficacy of this treatment.

Keywords: Acute myocardial infarction, left ventricular function, bone marrow-derived cells, cell therapy, bone marrow cells

Introduction

Despite rapid improvement in reperfusion strategies and medical treatment, acute myocardial infarction (AMI) and subsequent heart failure remain major causes of morbidity and mortality worldwide [1]. Former treatments such as medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting have increased the survival rate of patients with AMI. However, the results of AMI which include myocytes loss, absence of effective endogenous regenerative capacity, and damaged cardiac tissue could not be cured by traditional treatments [2]. Increase of ventricular dysfunction and heart failure post AMI has now become a severe medical problem which significantly affects the quality of life and is a major determinant for reduced life expectancy in patients after AMI [3].

Recently, stem cell therapy has emerged as a promising strategy for cardiac repair post AMI [4]. Numerous animal studies have indicated that transplantation of bone marrow-derived cells (BMCs) following AMI is associated with improvement in global and regional left ventricular (LV) function [4-7]. Subsequent experimental and early phase clinical studies have been promoted among patients with AMI to ascertain whether BMCs implantation following PCI would increase left ventricular ejection fraction (LVEF), improve LV volume, and prevent adverse clinical events. Some randomized clinical trials (RCTs) have suggested that BMC transplantation significantly improves global ejection fraction (EF) and attenuates adverse left ventricular remodeling and reduce severe clinical events post AMI [8, 9]. Others found mild or no improvement compared to the control groups [10, 11]. In addition, some studies have found

that BMCs treatment had short term effect on patients with AMI but the influence was lost during long term assessment [12]. However, others have argued that BMC therapy maintained a long term positive impact on patients [13]. These incongruent outcomes might be the result of small sample size, different patients side of the clinical trials, dose of cells infused into the patient, follow up time, measuring tools of the LV function, and types of cells.

Therefore, we conducted a meta-analysis of available prospective RCTs employing patients treated with intracoronary infusion of BMCs following PCI after suffering from ST-elevation myocardial infarction (STEMI) to assess the efficacy and safety of this treatment option and to evaluate the short-term and long-term effect of BMC therapy.

Method

Selection criteria

Studies were included in our analysis if: 1) Selected patients suffered from STEMI; 2) Patients were all under successful PCI before cell therapy; 3) Transplanted cells deriving from bone marrow with no restriction in term of types; 4) Study was RTCs with cell therapy group and control group; 5) Studies provided available LVEF data; 6) There are no other restrictions in terms of dose, time, or imaging modalities.

The exclusion criteria were as follows: 1) Trial design was not randomized; 2) Transplanted cells were not bone marrow derived cells or circulating/peripherals progenitor cells were mobilized by granulocyte colony stimulating factor (G-CSF) from bone marrows; 3) The trial was lack of control group; 4) There was no extractable data.

Data sources

We searched through PubMed and EMBASE databases between database inception and August 2017 for all potential articles. Clinical trials involved the same cohort of patients with sequential follow up durations or different outcomes were considered as one study. There was no overlap data in our analysis. The search was not limited to English-language literature.

The following trems were used: “bone marrow cells”, “stem cells”, “progenitor cells”, “cell therapy”, “cell transplantation”, “myocardial infarction”, “acute myocardial infarction”, “ST-elevation myocardial infarction”, “left ventricular ejection fraction” and all possible combinations. In addition, we manually searched the reference lists of all original articles and previous systematic reviews for other relevant papers.

Data extraction

Two investigators reviewed all of the titles and abstracts of the articles retrieved from the search independently, assessed the practicability of data collection, and confirmed quality rating. Relevant data were extracted from individual studied, when available, regarding baseline patients characteristics of both the cell therapy and the control group, stem cell type, infusion method, follow up time, injection time of cell therapy after symptom onset, dose of cells transplanted, infracted territory, imaging modality and parameter of LVEF at baseline and follow-up. When multiple imaging modes were applied in one study, the data measured by magnetic resonance imaging (MRI) and echocardiography (ECHO) were preferably used for primary analysiand subgroup analysis would be conducted with data extracted from each modality.

Data analyses

Pairwise meta-analysis was conducted to investigate the efficiency and safety of BMC therapy. In this study, pooled statistic were presented as weighted mean differences (WMD) with 95% confidence intervals (CI). I^2 was used to evaluate statistical heterogeneity. I^2 values of 25%-50%, 50%-75%, and >75% were considered evidence of low, moderate, and high statistical heterogeneity, respectively. If $P<0.05$ or $I^2>50\%$, a random effects model was applied for data calculation. Otherwise, a fixed effects model was selected. If significant heterogeneity was found ($I^2>50\%$), a sensitivity analysis would be performed. Funnel plots were plotted to assess possible publication bias. Results was considered statistically significant in the meta-analysis *when* $P<0.05$. The pooled analyses were performed with Review Manager 5.3 software.

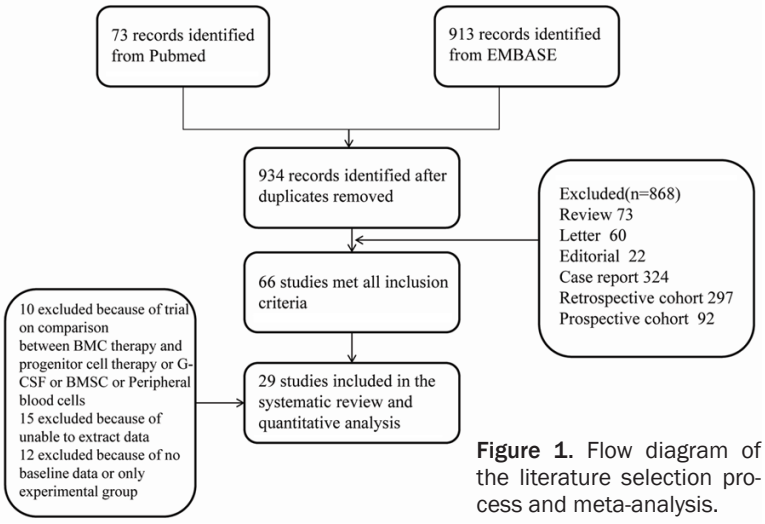

Figure 1. Flow diagram of the literature selection process and meta-analysis.

days after PCI. For outcome analysis, 10 studies provided LVEF data of less than 6 months follow up, 19 presented 6 months follow up, and 10 and 8 for 12 months and 18-60 months, respectively.

Among 29 studies, the majority applied freshly isolated bone marrow mononuclear cells (BMMC) isolated by density gradient separation of autologous BM aspirates. One trial utilized normoxia BMCs and one trial used BMMC plus G-CSF to mobilize endogenous cells.

Results

Search results

The electronic database identified 934 potential publications and the researchers further screened these studies for eligibility. After excluding 868 studies based on title and abstract, full-text analysis was performed on 66 articles. The outcome of interest was regarding demographic characteristics and LVEF outcomes at each follow up point. Of these 66 articles, 37 were excluded because the clinical trials were on comparison between BMC therapy and progenitor cell therapy or G-CSF or bone mesenchymal stem cells (BMSC) or peripheral blood cells mobilized by G-CSF (n=10), did not have available data (n=15), and no baseline data or only experimental group data (n=12). Finally, we included 29 studies for this meta-analysis (**Figure 1**).

Study characteristics

The 29 included studies enrolled a total of 3,099 participants, of which 1,634 patients were randomly assigned to BMCs group and 1,465 patients to the control group. **Table 1** summarizes the characteristics of each individual study [11, 14-41]. The enrolled studies were published from July 2004 to December 2015. The study sizes ranged from 10 to 176 patients and the follow up duration ranged from 1 week to 60 months. Of all included articles, number of infusion cells range from $<10^8$ to $>10^9$, most of them performed cell injection through intracoronary infusion 2 to 14

Less than 6 months follow up in LVEF

The results of pairwise analysis showed no difference in LVEF comparing BMCs group with control group within 6 months follow up. In two studies that provided 1 week LVEF data, no difference was observed between the therapy group and the control group (MD and 95% CI: 0.14 [-1.10, 1.39], I^2=0%, P=0.82). Also, there was no difference among 1 month (MD and 95% CI: 1.29 [-0.18, 2.76], I^2=71%, P=0.09), 3 months (MD and 95% CI: 1.90 [-0.46, 4.27], I^2=75%, P=0.12) and 4 months (MD and 95% CI: 0.88 [-0.74, 2.49], I^2=33%, P=0.29) follow up (**Figure 2**).

More than 6 months follow up in LVEF

Pooled data showed that the effect of BMCs therapy on LVEF emerged at 6 months and sustained up to 60 months follow-up. At 6 months follow up, BMCs group had a modest but significant increase (MD 2.73, 95% CI [1.15, 4.30], I^2=84%, P=0.0007) compared to control group. The effectiveness of cell therapy was even more profound at 12 months follow up (MD and 95% CI: 3.07 [1.48, 4.67], I^2=64%, P=0.0002). At long terms 18-60 months follow up, another significant improvement was observed in the BMCs group when compared to controls (MD and 95% CI: 2.37 [0.54, 4.20], I^2= 82%, P=0.0002) (**Figure 2**). Overall, to combine all of the LVEF data from all the time points, pooled statistic also revealed that LVEF in patients receiving BMCs was significantly augmented compared to control therapy (MD and 95% CI: 2.46 [1.47, 3.45], P=0.19).

Table 1. Population Characteristics

Author	Year	Cells type	BMMC (n)	Control (n)	Follow-up (months)	Doses	Injection Time	Infarcted Territory	Imaging
Assmus B	2014	BMMC	91	85	4	198×10^6	3-7 days	-	Angiography
Beitnes JO	2011	BMMC	50	50	3, 6, 12, 36	68×10^6	4-8 days	Anterior wall	ECHO
Benedek I	2014	BMCs	9	9	48	$1.66\pm0.32\times10^9$	3 weeks-3 months	Anterior wall	Angiography
Cao F	2009	BMMC	41	45	1, 3, 6, 12, 48	$5\pm1.2\times10^7$	7 days	Anterior wall	ECHO
Colombo A	2011	BMCs	5	5	12	5.9×10^6	10-14 days	Anterior wall	ECHO
Dill T	2009	BMCs	27	27	4, 12	$236\pm174\times10^6$	3-8 days	-	MRI
Ge J	2006	BMMC	10	10	1 week, 6	4.6×10^7	Within 24 hours	Anterior wall	MRI
Hirsch A	2011	BMMC	66	69	4	$296\pm164\times10^6$	3-8 days	Anterior wall	MRI
Hu X	2015	N-BMMC	11	14	6, 12	10×10^7	Day 5	Anterior wall	ECHO
Huang RC	2006	BMMC	20	20	1, 6	$1.8\pm4.2\times10^8$	Within 24 hours	Anterior wall	MRI
Huang RC	2015	BMMC	26	25	6, 12	4.9×10^8	3-7 days, 7-30 days	Anterior wall	ECHO
Huikuri V	2008	BMCs	40	40	6	360×10^6	2-6 days	Anterior wall	ECHO
Janssens S	2006	BMCs	33	34	4	304×10^6	Within 24 hours	Anterior wall	MRI
Lunde K	2006	BMMC	50	50	6	68×10^6	4-8 days	Anterior wall	SPECT
Meyer GP	2006	BMCs	30	30	6, 18	$24.6\pm9.4\times10^8$	4.8±1.3 days	Anterior wall	MRI
Nogueira FB	2009	BMMC	14	6	3, 6	100×10^6	5.5±1.28 days	Anterior wall	ECHO
Piepoli MF	2010	BMPC	19	19	1, 6, 12	418×10^6	4±1 days	Anterior wall	Rest SPECT
Plewka M	2011	BMCs	40	20	1, 6, 12, 24	$1.44\pm0.49\times10^8$	3-11 days	Anterior wall	ECHO
Roncalli J	2011	BMMC	52	49	3 months	$98.3+8.7\times10^6$	9.3±1.7 days	-	Angiography
San Roman JA	2015	BMMC/G-CSF	30	31	12	83×10^6	3-5 days	Anterior wall	MRI/Angiography
Schaefer A	2006	BMCs	30	29	6, 18, 60	$25\pm2\times10^9$	Within 5 days	Anterior wall	ECHO
Skalicka H	2012	BMCs	17	10	4 ,24	26.4×10^8	4-11 days	Anterior wall	ECHO
Srimahachota S	2011	BMMC	11	12	6	$420\pm221\times10^6$	57.2±122.8 days	-	MRI/ECHO
Tendera M	2009	BMMC	46	20	6	1.78×10^8	3-12 days	Anterior wall	MRI
Traverse JH	2011	BMMC	30	10	6	150×10^6	15.5-20 days	Anterior wall	MRI
Traverse JH	2012	BMMC	79	41	6	150×10^6	Day 3 or Day 7	-	MRI
Wollert KC	2004	BMMC	30	30	6	$24\pm6\times10^8$	4-8 days	-	MRI
Yao K	2009	BMCs	12	12	6, 12	$1.9\pm1.2\times10^8$	3-7 days	Anterior wall	MRI

BMMC, bone marrow mononuclear cells; BMCs, bone marrow-derived cells; N-BMMC, normoxia bone marrow mononuclear cells; BMPC, bone marrow progenitor cells; G-CSF mobilization, Granulocyte colony-stimulating factor mobilization; MRI, magnetic resonance imaging; ECHO, echocardiography; SPECT, single photon emission computed tomography.

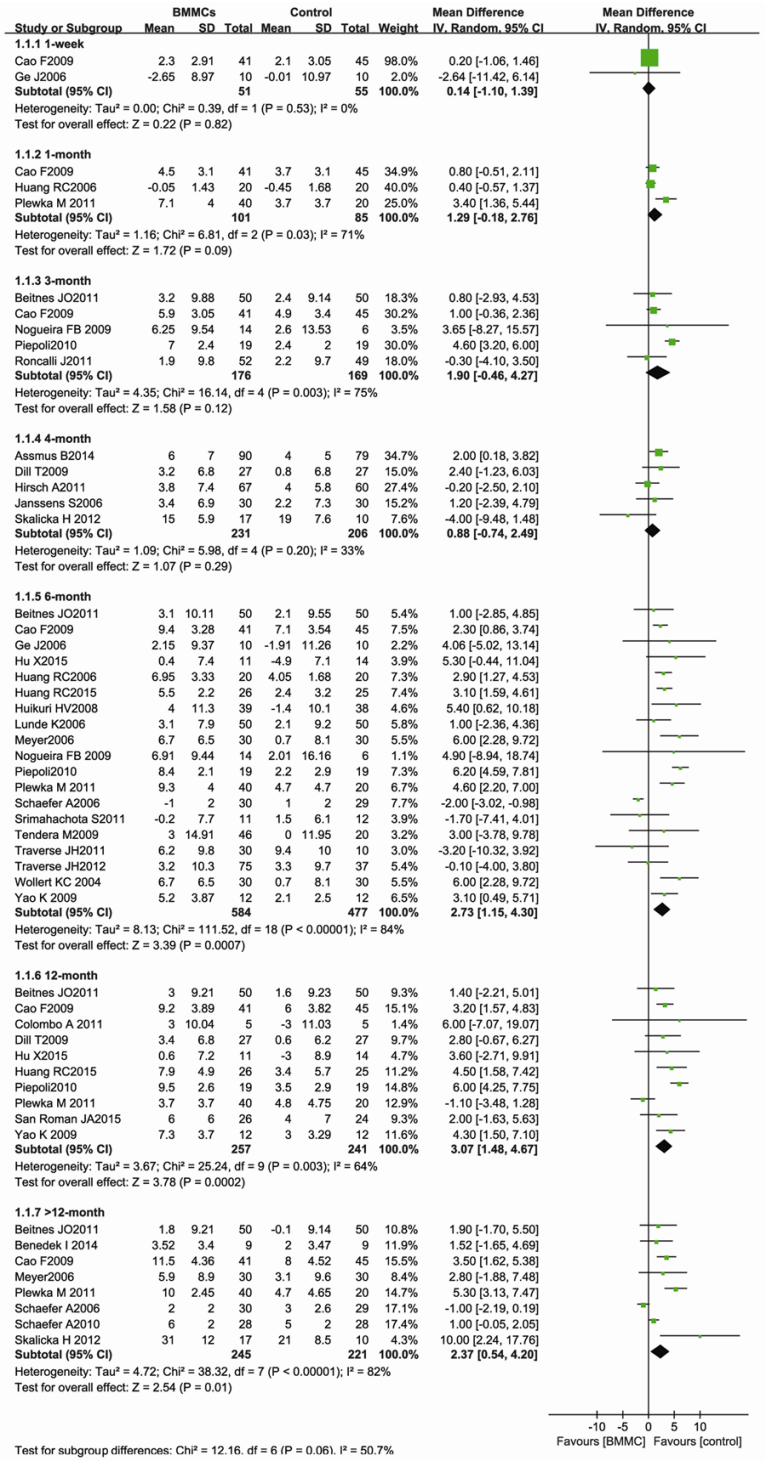

Figure 2. Improvement of LVEF in different time duration, 1 week, 1 month, 3 months, 4 months, 6 months, 12 months, and more than 12 months follow up. Forest plot of weight mean different (WMD), with 95% confidence interval (CI) in LVEF in patients treated with BMCs compared with controls.

Subgroup analysis

Since there was considerable heterogeneity of the LVEF parameters, we conducted a subgroup analysis to assess the influence of different measuring modalities on the LVEF results. As shown in **Figure 3**, 19 articles presented 6 months follow up data, of which 9 of them were measured by cardiac MRI and 10 were measured by ECHO. LVEF measured by cardiac MRI showed an increase on cell therapy group compared to control group (MD and 95% CI: 2.80 [1.13, 4.47], I^2=39%, P=0.001) and ECHO measurement also revealed a significant difference between the cell therapy group and control group (MD and 95% CI: 2.31 [0.19-4.42], I^2=84%, P=0.03). For the studies which provided 12 months LVEF data, 6 were measured by ECHO and 3 were measured by MRI. We found a trend for better LVEF improvement in favor of cell therapy group in both MRI (MD and 95% CI: 3.26 [1.39, 5.12], I^2=0%, P=0.0006) and ECHO (MD and 95% CI: 2.25 [0.14, 4.35], I^2=58%, P=0.04) subgroups (**Figure 4**).

Publication bias

A funnel plot for LVEF at 6 months, 12 months follow up indicated that studies were equally distributed around the overall estimate, suggesting no significant publication bias (**Figure 5**).

Discussion

In this article, we conducted a meta-analysis of comparative studies to assess the safety of BMCs transplantation therapy and the short-term and long-term effectiveness of BMC therapy for patients suffering from STEMI. Although numerous previous studies have explored in this areas, this study still has some superiorities. Our study included a large number of publica-

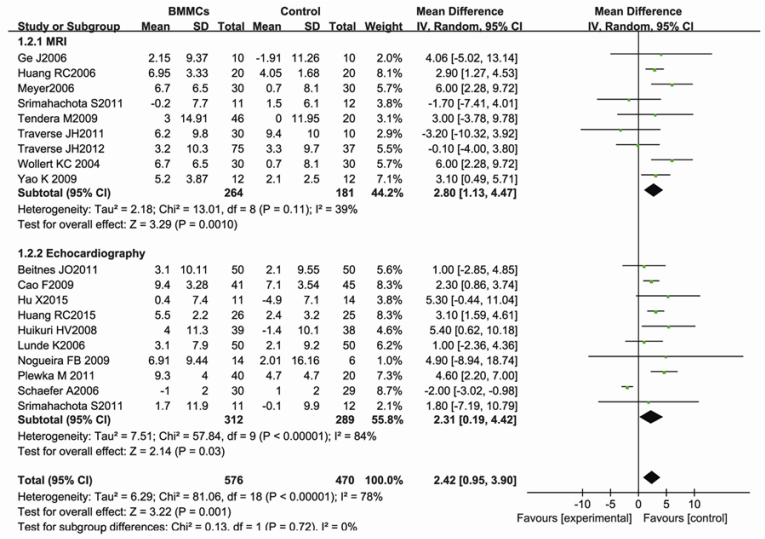

Figure 3. Comparison between MRI and ECG in LVEF 6 months follow up.

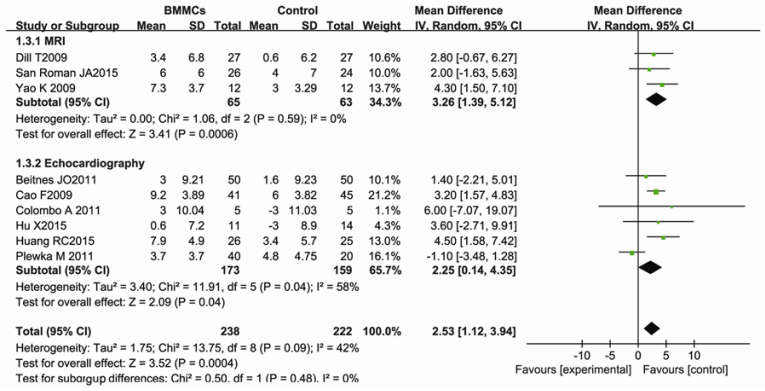

Figure 4. Comparison between MRI and ECG in LVEF 12 months follow up.

tions up to 29 RCTs demonstrating the latest clinical outcomes of LVEF in patients with STEMI receiving cell therapy. Most of the included studies uesed unselected BMMC as infusion cells. Because some articles argued that the potential beneficial effects could be attributed to the combined effects of all infused mononuclear cells, rather than the small amount of progenitor cell present in the bone marrow [42]. According to the pooled outcomes, BMC treatment led to a significantly better improvement of LVEF at 6 months compared to control therapy, and the beneficial effect sustained to 12 months and even 18 to 60 months follow up. These findings were in line with others meta-analysis which also suggested that cell therapy significantly ameliorate LVEF at 6 to 12 months [43, 44]. Our study also demonstrated that cell therapy had a long-term (up to 18-60 months) positive effect on LVEF on STEMI patients, which was inconsistent with a study by Lee [45], suggesting no significant difference between therapy group and control group at long-term follow up. A few studies also found long-term efficacy of BMC therapy in AMI patients [46, 47]. However, they only included a very small amount of studies. Our meta-analysis enrolled eight studies provided long-term follow up data, which made our result more robust. Some of the clinical trials argued that the number of BMCs administered had a positive association with the effect on LVEF. For studies using high dose BMC transplantation, the mean change in LVEF trend was statistically significant. Several previous trials indicated that significant effects on LVEF may only occur when the infusing doses are higher than 10^8 BMCs [48-50]. In our study, only six studies injected BMC less than 10^8 and the remaining trials infused doses higher than 10^8. Pooled outcomes showed that LVEF was increased significantly in patients received BMCs compared with controls in both lower and higher doses group (data not showed). The results suggested that doses of cells might have no influence on the effectiveness of BMCs.

Other studies suggested that the timing of BMCs transplantation after primary PCI has an effect on LVEF outcome. However, the studies regarding this aspect have shown controversial results. Jeevanantham et al. and Huang RC et al. investigated the timing of cell delivery and the results showed that the timing of cell transfer was not correlated with the effect of BMCs treatment on LVEF [48, 51]. In REPAIR-AMI trial and SWISS-AMI trials, the effects of BMC therapy tend to be more prominent when the cells

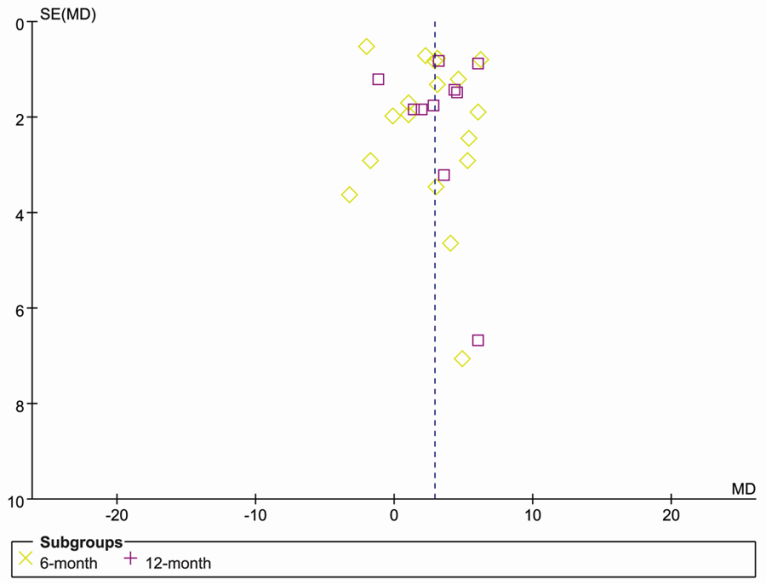

Figure 5. Funnel plot of left ventricular ejection fraction of included trials. SE (MD): standard error of mean difference; MD: mean difference.

infusion were performed at 5-7 days [19, 52]. Zimmet et al. demonstrated that cells transfer over 9 days post AMI did not appear to be associated with changes in LVEF [53]. Schachinger et al. randomized trial suggested that BMCs transplantation should be administrated more than 4 days post STEMI in order to obtain the best beneficial results from this treatment [54]. In the present meta-analysis, the majority of studies performmed intracoronary injection of BMC 2-14 days after PCI, and the results showed better LVEF recovery in BMCs group compared with controls. This finding indicated that 2-14 days after PCI might be the optimal time window for cell infusion.

We also assessed the influence of different measuring modalities on LVEF and observed that imaging modes might be one of the sources causing heterogeneity among studies. In 6 months and 12 months follow up, subgroup analysis based on MRI and ECHO was conducted. The results revealed that BMC treatment was still preferable to control therapy in improving LVEF according to both imaging measurement. However, the I^2 value dropped from high to moderate or even low when separating the results into MRI and ECHO. The subgroup anlysis on the other hand could strengthen the statistic power of our results. Further assessment should be conducted regarding this aspect to confirm the influence of measurement modality on LVEF results.

Since a number of initial studies have been revealed of cell therapy trials for AMI, considerable knowledge has been accumulated. However, there are still many challenges to achieving favorable clinical outcomes [55]. The incongruous clinical results of BMC therapy may be due to cell variability in patients related to a decrease in the number and potency of stem and progenitor cells. Also, these discrepancies may be caused by the timing of baseline LVEF recordings, the differences of functional LV measurement, cell processing strategy, and mechanisms of cell infusion [45].

Conclusions

We conducted a meta-analysis on RCTs of bone marrow-derived cell therapy for patients with STEMI. Although the effects of LVEF improvement were inconsistent in cases of different time duration, the results show that this therapy is safe and feasible. BMC therapy significantly improved LVEF at 6 month compared with controls and the beneficial effect could sustain to 5 years follow up. Further clinical trials should be conducted based on sufficient sample size, devoting more effort into detecting both short-term and long-term therapeutic outcomes by different measurement modalities to validate the efficacy of BMC therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Zhikuan Luo, Department of Intensive Care Unit, Tianjin Fourth Central Hospital, 3 Zhongshan Road, Tianjin 300140, China. Tel: +86-22-26249194; E-mail: zhikuanluo@163.com

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