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Impact of bone marrow mononuclear cells therapy on left ventricular function in patients with ST-elevated myocardial infarction

A meta-analysis

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Abstract

Background: Bone marrow mononuclear cell (BMMNC) therapy has been used as an adjunctive treatment in patients with ST-elevated myocardial infarction (STEMI). However, the therapeutic efficacy of this approach remains controversial. The present meta-analysis is aimed to evaluate the impact of cell therapy on left ventricular function after STEMI.

Methods: We searched through PubMed and EMBASE databases till 2017 for all relevant publications using certain search terms. Randomized controlled trials investigating the effect of BMMNC therapy in patients with STEMI who underwent percutaneous coronary intervention were selected. Wall motion score index (WMSI), infarct size, wall thickening, and myocardial perfusion were our endpoints.

Results: A total of 24 trials with 1536 patients were included in our study. Overall, as observed in our data, cell therapy reduced infarct size by −2.32 (95% confidence interval [CI] −4.03, −0.62; $P = .007$; $I^2 = 24\%$) and improved myocardial perfusion by −3.04 (95% CI −3.94, −2.15; $P < .001$; $I^2 = 0\%$). However, there was no significant difference between treatment group and control group in WMSI or wall thickening.

Conclusion: Intracoronary BMMNC infusion is safe for patients with STEMI. It is also associated with improvement of infarct size and myocardial perfusion. Further multicenter randomized trials should be conducted to validate the therapeutic efficacy of this treatment.

Abbreviations: AMI = acute myocardial infarction, BMMNCs = bone marrow mononuclear cells, LV = left ventricular, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, MRI = magnetic resonance imaging, PCI = percutaneous coronary intervention, RCTs = randomized controlled trials, SPECT = single photon emission computed tomography, STEMI = ST-elevated myocardial infarction, WMSI = wall motion score index.

Keywords: bone marrow mononuclear cells, infarct size, left ventricular function, ST-elevated myocardial infarction, wall motion score index

1. Introduction

Acute myocardial infarction (AMI) is the major cause of congestive heart failure and subsequent mortality worldwide. It is a serious complication of ischemic heart disease that inadequate blood supply to the heart muscle reaches its critical limit and subsequently leads to massive necrosis of cardiac cells.[1] Without proper treatment, AMI will cause loss of approximately 1 billion cardiomyocytes.[2] Unlike other human body tissues, heart tissue has a diminished ability to repair itself completely after AMI.[3] As a consequence, it will cause progressive cavitary dilation and negative remodeling on the left ventricle, and will significantly compromise cardiac contractility.[4] Despite optimal state-of-the-art pharmaceutical and therapeutic strategies, the prognosis of AMI remains dubious.[5,6]

Cell-based therapy has emerged as an alternative therapy to complement primary percutaneous coronary intervention (PCI) or thrombolytic therapy in the prevention of congestive heart failure after AMI. More than a decade after the first patient was treated with intracoronary infusion of unselected bone marrow-derived mononuclear cells (BMMNCs),[7] numerous clinical studies were conducted to investigate the feasibility and efficiency of cell-based therapy in patients with AMI. Many studies have repeatedly confirmed the safety and feasibility of cell therapy. However, the effectiveness of this treatment remains controversial. A number of clinical trials suggested that cell therapy could improve left ventricular (LV) function and prevent adverse LV remodeling,[8,9] whereas other studies showed ambiguous or even negative results.[10,11] Interestingly, most of the clinical trials evaluated the effectiveness of cell therapy by accessing clinical parameters regarding left ventricular ejection fraction (LVEF),

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left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV).[12] However, other parameters such as wall motion, wall thickening, infarct size, and myocardial perfusion can also be served as precise indicators to estimate the efficiency of BMMNC therapy.

Several studies had been performed to investigate the relationship of wall motion, wall thickening, and infarct size with LV performance after AMI. A research reported that infarct size and depression of LV performance were well correlated. Smaller infarct size resulted in less depression of LV performance.[13] A study on the value of admission wall motion score in AMI indicated that higher wall motion score resulted in higher mortality.[14] Another study concluded that wall thickening parameter could provide additional information for the prediction of LV functional recovery.[15]

The current meta-analysis aims to assess the influence of BMMNC therapy in patient with ST-elevated myocardial infarction (STEMI) by analyzing the change in wall motion score index (WMSI), infarct size, wall thickening, and myocardial perfusion after cell therapy.

2. Methods

2.1. Search strategy

Randomized controlled trials (RCTs), exploring the impact of BMMNC therapy on STEMI patients, were identified from PubMed and EMBASE databases between 2004 and 2017. The search terms used for the retrieval of relevant studies were as follows: bone marrow mononuclear cells, bone marrow cells, BMC, infarct size, wall motion, wall motion score index, wall thickening, myocardial perfusion, acute myocardial infarction, ST-elevation myocardial infarction, AMI, STEMI, cell therapy, randomized trials, and all possible combinations. Reference lists of identified articles, reviews on the topic for further eligible trials, and recently published editorials were also searched for additional studies. There was no restriction in terms of year of publication, language, or publication status.

2.2. Inclusion criteria

Studies that met the following criteria were eligible for inclusion in the meta-analysis: study was RCT; participants with clinical diagnosis of STEMI; patients under primary PCI before cell transplantation; the intervention consisted of BMMNCs freshly isolated without restriction on doses or timing of administration; in the comparator arm, patients did not receive BMMNCs (eg, control media or plasma); co-interventions were allowed while they were equally applied in each treatment group; and studies included proper outcome of WMSI, wall thickening, infarct size, and myocardial perfusion. Trials that did not meet the above criteria, duplicate reports, and ongoing studies were excluded. Authors did not conduct any experiment on humans or animals by themselves in the meta-analysis. Therefore, the ethical approval was not applicable.

2.3. Data extraction

Eligibility screening, data extraction, and assessment of methodological quality were undertaken by 2 reviewers independently. Data including first author, year of publication, injected cell types, nature of the intervention, study design, imaging modality, and clinical and imaging outcomes were obtained from the original publications. The primary endpoints of our study were the mean changes of WMSI and infarct size from baseline to follow-up. Secondary endpoints were changes in wall thickening and myocardial perfusion. The quantitative information about endpoints in each treatment group was obtained by extracting the mean change ± SD from the studies.

When several imaging methods were used for outcome assessment, magnetic resonance imaging (MRI) and echocardiography data were preferentially selected in the analysis, followed by single-photon emission computed tomography (SPECT) and LV angiography. Infarct size was preferably collected in % of LV or grams when available. Additionally, subgroup analyses were performed in our study to gain more insight into possibly discriminating parameters or conditions that might improve the outcome in future trials. The conducted subgroup analyses included: follow-up duration of 4, 6, 12, and 18 to 60 months; LVEF at baseline ($\leq$50%, >50%);

2.4. Statistical analysis

The meta-analysis was performed at the start time by adjusting changes in WMSI, wall thickening, infarct size, and myocardial perfusion in both therapy group and control group via Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. Outcomes were analyzed with random-effects models. Summarized results were presented as weighted mean difference with 95% confidence interval (CI) per clinical outcome. We presented each outcome split for different follow-up duration (4, 6, 12, and 18–60 months).

Heterogeneity was examined using the I^2 statistic. I^2 >50% was considered significant heterogeneity among trials. We explored the potential reasons for the observed heterogeneity with particular emphasis placed on follow-up time, measuring modality and baseline characteristics differences among the included studies. Pooled outcome of each endpoint was displayed using forest plots. P values <.05 was considered as statistically significance.

3. Results

3.1. Search results

Of the 954 potential articles identified during the initial search, 868 citations were excluded based on title and abstract. Full-text analysis was performed in the remaining 86 studies. Among the articles retrieved in completed form, 23 were excluded for investigating different endpoints, 8 for lack of control group, 5 for irretrievable or unclear data, and 11 for studying intracoronary cell therapy for heart failure or chronic myocardial ischemia. In addition, 7 nonrandomized trials, 5 studies using granulocyte-colony stimulating factor treatment, and 3 studies using allogeneic human mesenchymal stem cells were also excluded. Eventually, 24 RCTs with a total of 1536 patients were enrolled in our meta-analysis (Fig. 1).

3.2. Study characteristics

Table 1 summarized the basic characteristics of each individual study. The selected studies were published between 2004 and June 2015. Study size ranged from 10 to 135 patients. The majority of clinical trials used a 1:1 randomization scheme. Among them, 13 trails provided WMSI, 5 studies measured wall thickening data, 9 presented infarct size parameter, and 4 assessed myocardial

Table 1

Population characteristics.

Study	Year	Design	Primary intervention	Cells type	Patients Enrolled	Follow-up (mos)	Imaging
Beitnes et al[16]	2011	RCT	PCI	BMMNCs	100	3, 6, 12, 36	ECHO
Cao et al[17]	2009	RCT	PCI	BMMNCs	96	3, 6, 12, 48	ECHO
Colombo et al[18]	2011	RCT	PCI	BMMNCs	10	12	ECHO
Dill et al[19]	2009	RCT	PCI	BMMNCs	54	4, 12	MRI
Hirsch et al[20]	2011	RCT	PCI	BMMNCs	135	4	MRI
Hu et al[21]	2015	RCT	PCI	BMMNCs	25	6, 12	ECHO
Huang et al[22]	2015	RCT	PCI	BMMNCs	51	6, 12	ECHO
Huikuri et al[23]	2008	RCT	PCI	BMMNCs	80	6	ECHO
Janssens et al[24]	2006	RCT	PCI	BMMNCs	67	4	MRI
Lunde et al[25]	2006	RCT	PCI	BMMNCs	100	6	SPECT
Meyer et al[26]	2006	RCT	PCI	BMMNCs	60	6, 18	MRI
Miettinen et al[27]	2011	RCT	PCI	BMMNCs	80	6	Angiography
Piepoli et al[28]	2010	RCT	PCI	BMMNCs	38	1, 6, 12	Rest SPECT
Plewka et al[29]	2009	RCT	PCI	BMMNCs	46	6	ECHO
Roncalli et al[30]	2011	RCT	PCI	BMMNCs	101	3	Angiography
San Roman et al[31]	2015	RCT	PCI	BMMNCs	61	12	MRI/angiography
Schaefer et al[32]	2006	RCT	PCI	BMMNCs	59	6, 18	ECHO
Schaefer et al[33]	2010	RCT	PCI	BMMNCs	59	60	ECHO
Skalicka et al[34]	2012	RCT	PCI	BMMNCs	27	4,24	ECHO
Srimahachota et al[35]	2011	RCT	PCI	BMMNCs	23	6	MRI/ECHO
Traverse et al[36]	2012	RCT	PCI	BMMNCs	120	6	MRI
Trzos et al[37]	2009	RCT	PCI	BMMNCs	60	1	ECHO
Wollert et al[38]	2004	RCT	PCI	BMMNCs	60	6	MRI
Yao et al[39]	2009	RCT	PCI	BMMNCs	24	6, 12	MRI

BMMNCs = bone marrow mononuclear cells, ECHO = echocardiography, MRI = magnetic resonance imaging, PCI = percutaneous coronary intervention, RCT = randomized controlled trials, SPECT = single-photon emission computed tomography.

perfusion.[16–39] Imaging modalities of the enrolled studies included MRI, SPECT, echocardiography, radionuclide angiography, and LV angiography. Cardiac parameters measured by the above appliances were considered equivalent.

3.3. Mean differences in cardiac parameters

Overall, we observed no significant treatment-related differences in WMSI (−0.02; 95% CI −0.05 to 0.02; $P = .40$; $I^2 = 49\%$; Fig. 2) or wall thickening (−1.11; 95% CI −2.31 to 0.08; $P = .07$; $I^2 = 51\%$; Fig. 3) between control group and BMMNC therapy patients. On the contrary, a significant improvement in infarct size (−2.32; 95% CI −4.03 to −0.62; $P = .007$; $I^2 = 24\%$; Fig. 4) and myocardial perfusion (−3.04; 95% CI −3.94 to −2.15; $P < .001$; $I^2 = 0\%$; Fig. 5) was noticed.

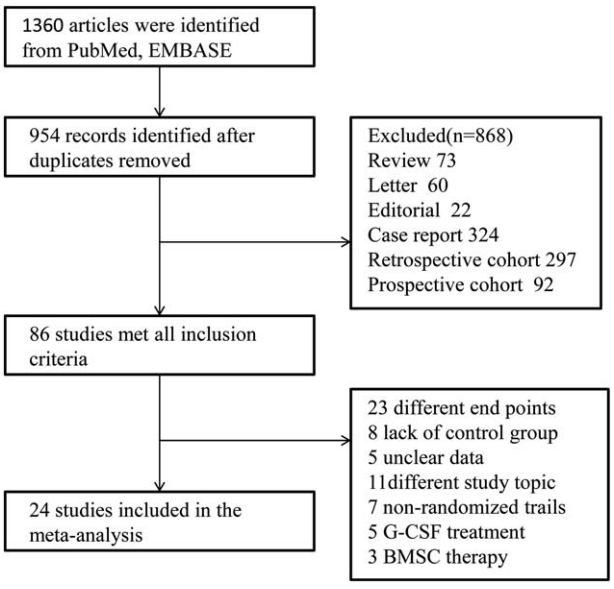

Figure 1. Flow diagram of the literature selection process and meta-analysis.

3.4. Effects of BMMNC therapy over time

Although we found no overall beneficial effect in WMIS toward the cell treatment group, a significant decrease was found in 18 to 60 months' follow-up (−0.09; 95% CI −0.15 to −0.03; $P = .002$; $I^2 = 0\%$; Fig. 2) when adjusting the outcomes according to different time duration. At 4 months follow-up in infarct size, there was no difference between treatment group and control group (2.72; 95% CI −7.58, −2.14; $P = .27$; $I^2 = 70\%$; Fig. 4). However, a significant reduction was detected in 6 months (−2.50; 95% CI −4.82 to −0.17; $P = .04$; $I^2 = 0\%$; Fig. 4) and 18 to 60 months (3.45; 95% CI −6.01 to −0.89; $P = .008$; $I^2 = 0\%$; Fig. 4) follow-up.

3.5. LV function at baseline

According to our data, patients with a lower LVEF (≤50%) at baseline did not benefit more from cell therapy compared with patients with a higher LVEF (>50%) on WMIS. However, the beneficial effect of BMMNC treatment on infarct size was significantly greater in patients with a lower LVEF (≤50%) at baseline (−3.00; 95% CI −5.72, −0.28; $P = .03$; $I^2 = 47\%$; Table 2), as opposed to no reduction in patients with a LVEF >50% (−1.11; 95% CI −3.33, 1.10; $P = .32$; $I^2 = 0\%$; Table 2).

4. Discussion

The main finding of the present study was that intracoronary cell therapy as a compensating treatment after PCI in patients post

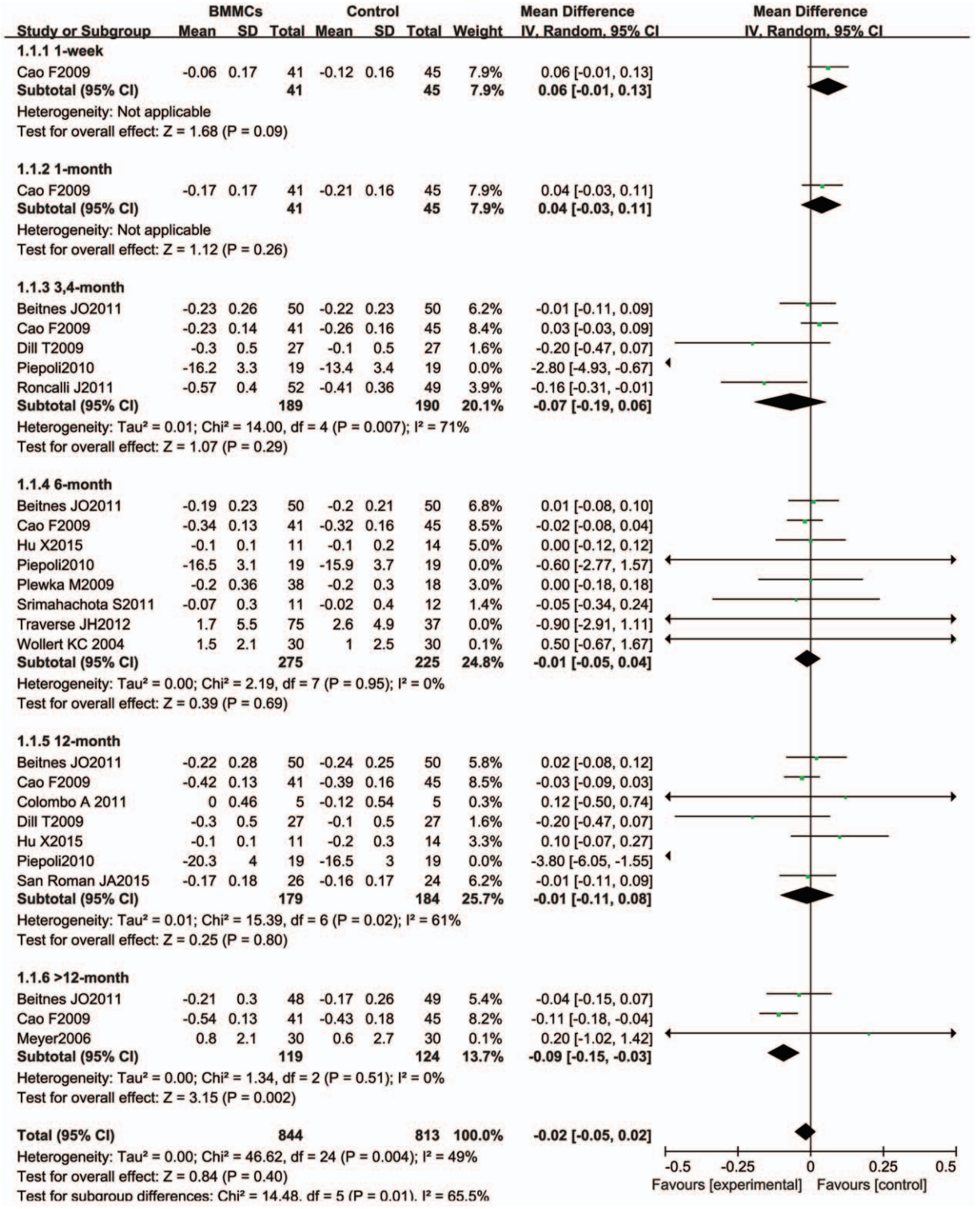

Figure 2. Forest plot of changes in wall motion score index.

STEMI resulted in a significant decrease in infarct size compared with control group, whereas no improvement was observed in WMSI. In addition, analysis of secondary endpoints showed significant improvement on myocardial perfusion in patients receiving BMMNCs. However, it did not improve wall thickening in comparison between treatment group and control group. Furthermore, in subgroup analysis, results showed that the effect of cell transplantation on wall motion did not exist at 4 to 12 months' follow-up, but emerged at 18 to 60 months' follow-up by a slight reduction in WMSI. This finding indicated that cell therapy might have a long-term profitable effect in patients with STEMI. Pooled analysis also revealed that the benefit of cell therapy on infarct size occurred at 6 months' follow-up and sustained to 18 to 60 months' follow-up, which implied

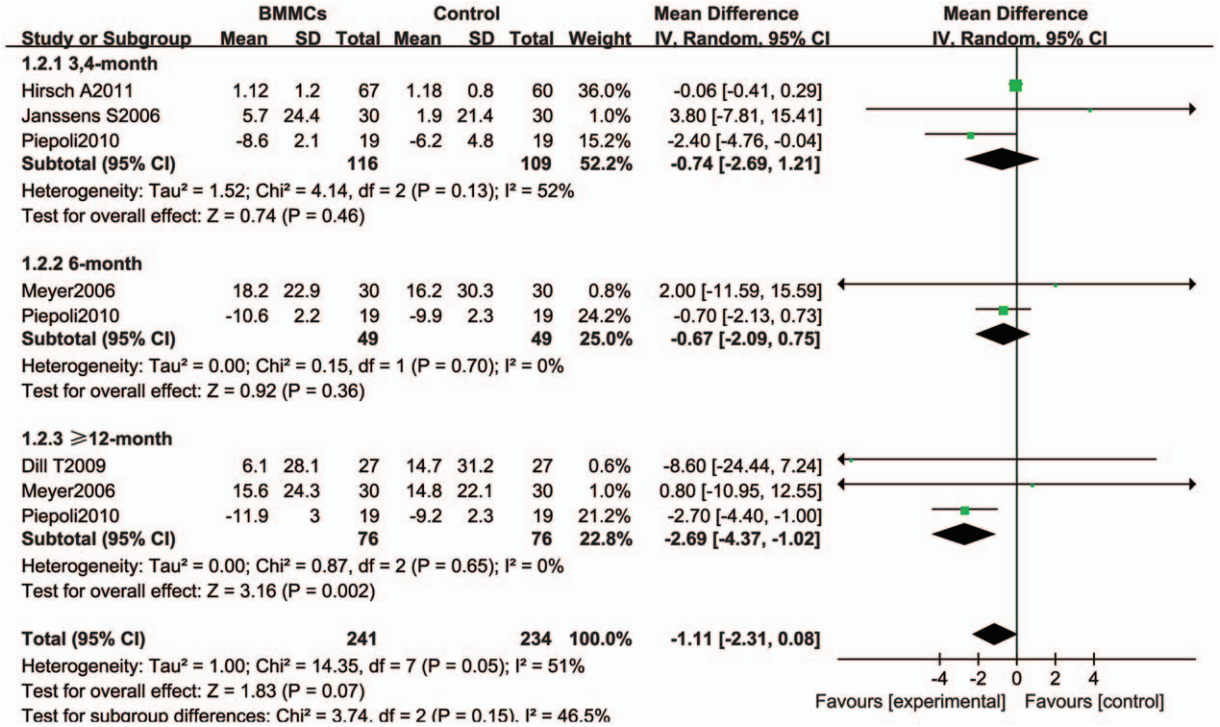

Figure 3. Forest plot of changes in wall thickening.

BMMNCs had both short-term and long-term positive influence on STEMI.

Because cell therapy was considered as an available treatment for patients suffering from STEMI, numerous clinical trials were performed on animals, and also humans, to assess the feasibility and validity of this treatment option. The majority of studies used cardiac parameters such as LVEF, LVEDV, and LVESV to identify the function of cell therapy. However, researchers found

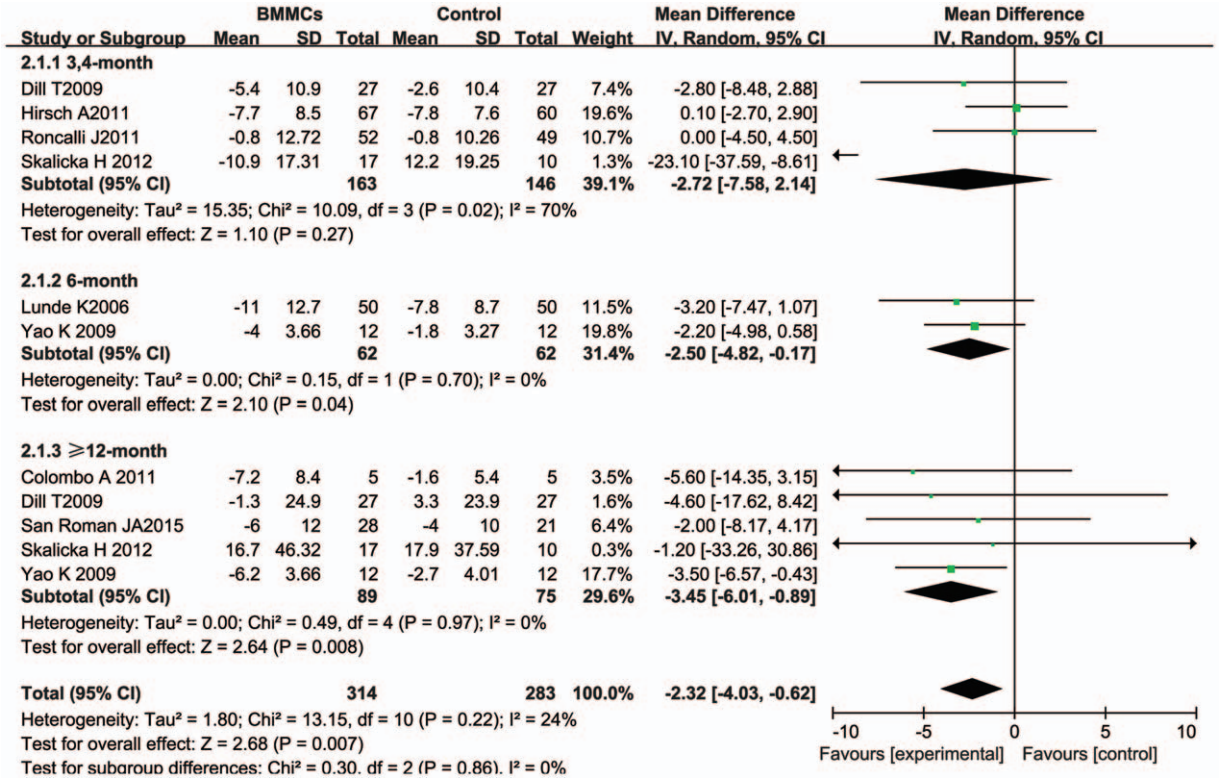

Figure 4. Forest plot of changes in infarct size.

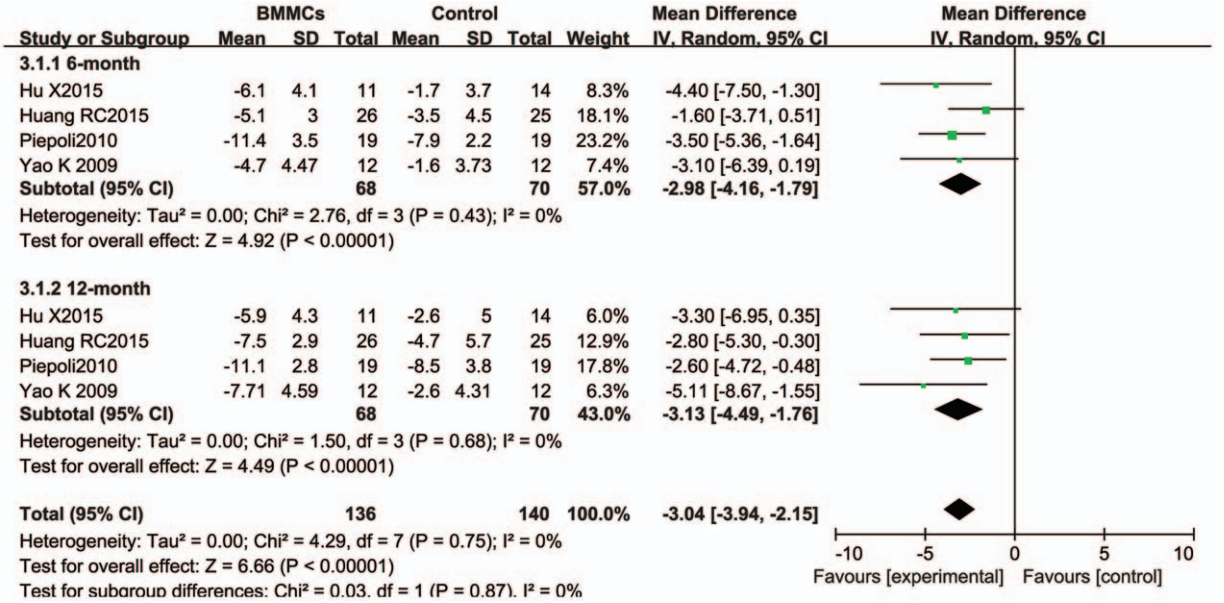

Figure 5. Forest plot of changes in myocardial perfusion.

that these indices had limited sensitivity to provide accurate and reliable diagnosis for patients at the early stage of disease development as the changes in cardiac function was rather localized instead of globalized. Furthermore, infarct zone of the myocardium tended to become rigid and thinner as a result of injury and necrosis.[40] Therefore, regional assessment of WMSI, infarct size, wall thickening, and myocardial perfusion might provide a mean to improve clinical diagnosis for better patient outcomes.

Regional assessment of WMSI, infarct size, and wall thickening has recently received more attention for researches, especially in terms of focal myocardial disease including AMI. Several previous studies demonstrated the relationship between these clinical indexes and AMI. A study of WMSI for risk stratification after AMI concluded that WMSI had a greater power in the prediction of the combined endpoint of death, congestive heart failure, and unstable angina than LVEF.[41] An article focused on infarct size indicated that larger infarct size after AMI was associated with increased mortality risk.[42] Another study showed that wall thickening was closely related to cardiac function and could reveal regional abnormality triggered by AMI.[40]

The current meta-analysis focused on the changes in WMIS, infarct size, wall thickening, and myocardial perfusion after BMMNC therapy. Pooled outcome showed that infarct size significantly reduced in cell therapy group compared with control group. This finding was corresponding with 2 previous meta-analyses which observed a reduction by −5.6% (95% CI −8.7, −2.5; $P<.001$),[43] and −2.69% (95% CI −4.83, −0.56; $P=.01$)[44] in infarct size with the follow-up duration of more than 3 months. However, we found no improvement in wall motion and wall thickening. It was opposite to an analysis that found significant decrease in cell treatment group.[45] These inconsistency occurred might on account of different cell types, dose of cell infusion, administration routes, or different imaging modalities. Further investigations are required to verify the effect of cell therapy after STEMI.

Some limitations still existed in our meta-analysis. Our study did not restrict patients' baseline characteristics such as timing of cell transplantation, number of cells injected, and imaging modalities due to limited number of studies enrolled in the meta-analysis. This might be 1 of the reasons causing high heterogeneity among studies. Furthermore, our analysis included small-sized studies, and studies with different cell isolation protocols and cell storage methods which might be another source of heterogeneity. Meanwhile, it should be emphasized that the conclusions of the present analysis were confined only to intracoronary BMMNC transfer after STEMI. The effectiveness of other stem cell types remains to be established.

5. Conclusions

Our meta-analysis further proves the safety and feasibility of BMMNC therapy on STEMI patients. Cell therapy for STEMI is

Table 2

Subgroup analysis of bone marrow mononuclear cells.

	No. of RCTs	WMSI		Infarct size	
		Difference in mean	*P*	Difference in mean	*P*
EF before infusion					
EF ≤50%	9	−0.34 (−0.76, 0.07)	.10	−3.00 (−5.72, −0.28)	.03
EF >50%	15	−0.01 (−0.03, 0.02)	.63	−1.11 (−3.33, 1.10)	.32

EF = ejection fraction, RCT = randomized controlled trial, WMSI = wall motion score index.

still promising in reducing infarct size and improving myocardial perfusion. Further, adequately powered trials using optimal dosing, longer-term outcome assessments, and more reliable and more patient-centered study design are required.

Author contributions

Conceptualization: Chao Wang.
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Investigation: Chao Wang, Xiujiang Han.
Methodology: Chao Wang, Xiujiang Han, Yongjian Li, Boya Zhang.
Project administration: Chao Wang.
Software: Yongjian Li, Boya Zhang.
Validation: Chao Wang.
Visualization: Chao Wang.
Writing – original draft: Chao Wang, Xiujiang Han.
Writing – review & editing: Chao Wang.

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