Review Article
Efficacy and safety of mesenchymal stromal cells on left ventricular function after acute myocardial infarction: a meta-analysis of randomized controlled trials

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Abstract: Mesenchymal stromal cells (MSCs) transfer has emerged as a new therapeutic modality for acute myocardial infarction (AMI), but the benefits and safety profile still remain controversial. We performed a meta-analysis to assess the efficacy and safety of MSCs transplantation in patients with AMI based on published randomized controlled trials (RCTs). A systematic literature search of Pub Med, EMBASE, and the Cochrane library from 1985 to 2016 was conducted. We identified RCTs involving subjects with AMI receiving MSCs therapy and following up for at least 3 months for inclusion. Pooled analyses were conducted using random effects models. The defined end points were left ventricular ejection fraction (LVEF), left ventricular end-diastolic volumes (LVEDV) and left ventricular end-systolic volumes (LVESV), and major adverse cardiac event rates (MACEs). Seven trials with a total of 435 participants were included. Overall, MSCs therapy improved LVEF by 4.79% (95% confidence interval [CI] 2.12-7.46, P=0.0004), compared with the controls. There were trends toward reduced LVEDV and LVESV, but the differences were not significant (P=0.22 and P=0.09). Meta-analysis of the RCTs did not detect an association between MSCs and MACEs, all-cause death, heart failure, in-stent thrombosis, recurrent myocardial infarction, arrhythmia or re-hospitalization. In addition, Subgroup analysis also revealed greater increase in LVEF in favor of MSCs regarding duration of <6 months, 6 months and 12 months (P<0.00001, P=0.0003, P=0.0005, respectively) but not for >12 months (P=0.17) no matter what measurement was used. Based on the current clinical trials, transplantation of MSCs for patients with AMI induces a significant increase in LVEF and is safe in short-term follow-up.

Keywords: Mesenchymal stromal cells, acute myocardial infarction, left ventricular function

Introduction

Acute myocardial infarction (AMI) remains the leading cause of death worldwide despite remarkable progress in treatment and health care. Myocardial injury begins after 15-20 minutes of coronary artery occlusion and the procedure is irreversible [1]. The final result is necrosis and permanent loss of cardiomyocytes and the formation of scar tissue, which limit the ability to regenerate the lost cells. Although development of thrombolytic agents, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) can relieve the cause of the infarction, how to recuperate injured myocytes or regenerate new

ones can't be solved. Therapy with stem cells with potential to regenerate damaged myocardium during AMI has emerged as a novel alternative option.

Mesenchymal stromal cells (mesenchymal stem cells; MSCs), a new cell source for regenerative therapy, are a heterogeneous group of cells that can be isolated from many adult tissue (e.g. bone marrow, adipose tissue, umbilical cord) and culture expanded [2]. They have self-renewal and multi-lineage differentiation capabilities [3], regeneration of all cell types in the tissue where they are located [4]. Thus, the mechanism for MSCs therapy is based on the assumption that the transplanted cells may

have the potential to either transform into cardiomyocytes, hence replacing lost tissue, or repair the injured vascular and cardiac cells through paracrine effects [5-8].

Recently, there is a growing body of meta-analysis demonstrating the efficacy and safety of bone morrow stem cells (BMSCs) in patients with AMI and CAD, the results showed an improvement of cardiac function and a good security [9-11]. Meta-analysis regarding bone marrow-derived mononuclear cell (BMMNC) for the treatment for AMI indicated that intracoronary infusion of BMMNC is safe, but does not enhance cardiac function, nor does it improve clinical outcome [12]. A systematic review and meta-analysis of clinical trials in participants with clinical conditions of ischemic stroke, Crohn's disease, cardiomyopathy, myocardial infarction, graft versus host disease, and healthy volunteers revealed that MSC therapy appears safe [13]. However, the efficacy and safety of MSCs in patients with AMI are not known very well. Therefore, we conducted a meta-analysis to accurately evaluate the efficacy and safety of MSCs for patients with AMI on the basis of collective data from published randomized controlled trials (RCTs).

Materials and methods

Search strategy

We conducted literature searches form database of Pub Med (1985-2016), Embase (2003-2016), and the Cochrane library 2003-2016). The following search strategy was applied: mesenchymal stromal cells, mesenchymal stem cells, mesenchymal progenitor cells, bone marrow stromal cells, bone marrow mesenchymal stem cells, coronary artery disease, myocardial infarction, acute myocardial infarction. In addition, we manually searched the reference lists of all original articles and previous systematic reviews. Only articles published in English were included (**Table 1**).

Eligibility criteria

Studies were included based on the following criteria: (1) published RCTs, (2) conducted in patients were clinically diagnosed with AMI<1 month, (3) participants in control group received standard revascularization therapy or standard revascularization therapy with saline rather

than MSCs, (4) MSCs were derived from bone marrow, or umbilical cord, (5) the transplanted MSCs were purified autologous or allogeneic source, (6) MSCs were administered by intracoronary or intravenous injection, (7) no restrictions of MSCs dose. The exclusion criteria for studies were as follows: (1) patients were diagnosed with chronic ischemic heart disease, angina, old myocardial infarction (OMI), or coronary chronic total occlusion (CTO), (2) transplanted cells were other stem cell type other than MSCs, (3) circulating MSCs were mobilized from bone marrow with granulocyte colony stimulating factor (G-CSF), (4) no LVEF data were available, (5) less than 3 months of follow-up were recorded, (6) data were presented as median and range, or (7) publications were in languages other than English.

Data extraction

Two reviewers independently screened all titles, abstracts or article to identify studies that met the inclusion criteria. Discrepancies were resolved by consensus. Relevant data regarding study information, baseline characteristics, follow-up period, change in mean left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV), and major adverse cardiac events (MACEs) were extracted from individual studies. Clinical trials with multiple publications, sequential follow-up durations or different outcome indicators were considered as a single study. Give the multiple modalities used for their assessment, magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) data were preferred over echocardiographic data for primary analysis if available.

Study outcomes

The primary end point was mean LVEF changes from baseline to follow-up. Changes in mean LVEDV, LVESV, and the incidence of MACEs were considered as the secondary endpoints.

Statistical analysis

To assess risk of bias, assessment of the quality of studies was made in randomized trials which are based on the generation of random sequence, concealment of treatment allocation, blinding of participants and personnel, blinding of outcome assessors, incomplete out-

Table 1. Characteristics of studies included in the meta-analysis

| First authour (year)	Patients (T/C)	Age (years ± SD) (T/C)	Primary intervention	Cell type	Cell number (× 10^6)	Time to application after AMI (days)	Route of delivery	Duration (months)	Imaging modality
Chen (2004)	69 (34/35)	58±7/57±5	PCI	Autologous BMSCs	48000-60000	18	Infarct-related artery	3, 6	LVG/SPECT/ECHO
Chullikana (2015)	20 (10/10)	47.31±12.10/47.79±6.48	PCI	Allogeneic BMSCs	2 cells/kg	2	Intravenous	6, 24	SPECT/MRI/ECHO
Gao (2013)	43 (21/22)	55.0±1.6/58.6±2.5	PCI	Autologous BMSCs	3.08±0.52	16.6-17.6	Infarct-related artery	6, 12, 24	SPECT/ECHO
Gao (2015)	116 (58/58)	57.3±1.3/56.7±1.7	PCI	Allogeneic WJMSCs	6	5-7	Infarct-related artery	4, 12, 18	PET/SPECT/ECHO
Hare (2009)	60 (39/21)	59.9±12.3/55.1±10.2	PCI	Allogeneic BMSCs	3 groups receiving 0.5, 1.6, and 5 cells/kg respectively	9.8	Intravenous	1, 2, 3, 6, 12	ECHO/MRI
Lee (2014)	69 (33/36)	53.9±10.5/54.2±7.7	PCI	Autologous BMSCs	72±9	28.8	Infarct-related artery	6	SPECT/ECHO
Wang (2014)	58 (28/30)	58.0±10.2/56.1±9.8	PCI	Autologous BMSCs	200	22	Infarct-related artery	1, 3, 6	LVG/ECHO

Data are expressed as mean (SD). SD, standard deviation. T, treatment group; C, control group. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; BMSCs, bone-derived mesenchymal stem cells; WJMSCs, wharton's jelly-derived mesenchymal stem cells. MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; LVG, left ventriculography; ECHO, echocardiography.

Table 2. Quality assessment of study methodologies

RCT	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting
Chen (2004)	U	U	U	U	L	L
Chullikana (2015)	L	L	L	L	L	L
Gao (2013)	L	L	L	L	H	L
Gao (2015)	L	L	H	L	L	L
Hare (2009)	L	L	L	L	H	L
Lee (2014)	U	U	H	L	H	L
Wang (2014)	U	U	U	L	L	L

L = low risk of bias, H = high risk of bias, U = unclear risk of bias.
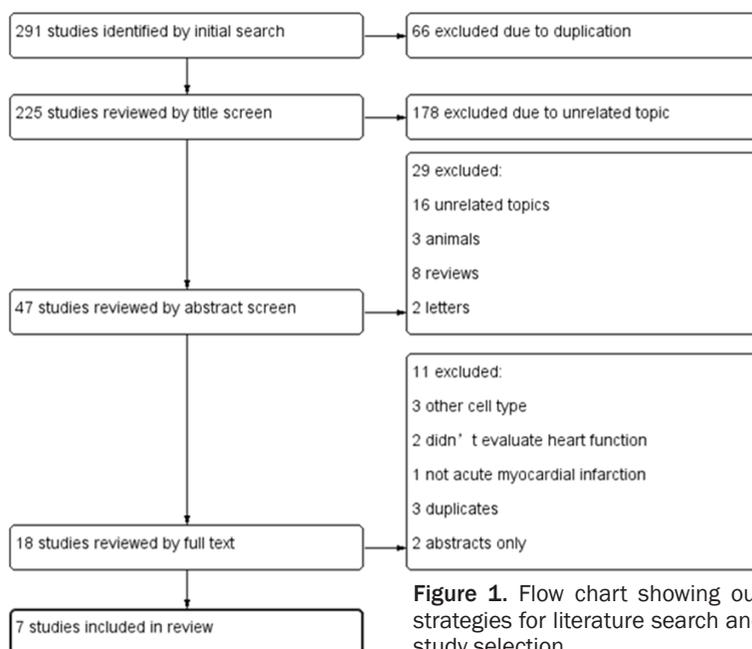
Figure 1. Flow chart showing our strategies for literature search and study selection.

were explored with subgroup analyses based on different duration of follow-up. Odds ratios (ORs) were calculated for clinical outcomes of MACEs, all-cause death, heart failure, in-stent thrombosis, recurrent MI, revascularization, arrhythmia and rehospitalization. Funnel plots were constructed to explore possible publication bias. A *P* value <5% was considered as statistically significant. Methodological quality and all analyses of outcome data were conducted using Cochrane Review Manager 5.3.

Subgroup and sensitivity analyses

come data, selective reporting and other bias (**Table 2**).

Statistical analyses were done in accordance with the PRISMA statement [14]. Continuous outcomes were expressed as weighted mean differences with 95% confidence intervals (CI). For most studies reporting mean ± SD at baseline and follow-up, but not the actual change (from baseline to follow-up) as mean ± SD, changes in SD were estimated according to a previously used standardized formula [15]. In the presence of significant heterogeneity, a random effects model was used to pool the data; otherwise, a fixed effects model was used. Data were analyzed for heterogeneity by I^2 statistic, which was defined as low (25%-50%), intermediate (50%-75%), or high (>75%). Potential reasons for observed heterogeneity

Additional subgroup analyses were performed within the RCTs based on the duration of follow-up in an attempt to gain more insight into possible discriminating parameters or conditions that might improve outcome in future trials. The small number of RCTs in each meta-analysis precluded the conduct of planned sensitivity analyses.

Results

Search results

The initial search identified 291 citations using the search strategies met the inclusion criteria (**Figure 1**); the numbers were reduced to 225 after removal of duplications, 207 were excluded based on the title and abstract screen, the remaining 18 studies were assessed for eligi-
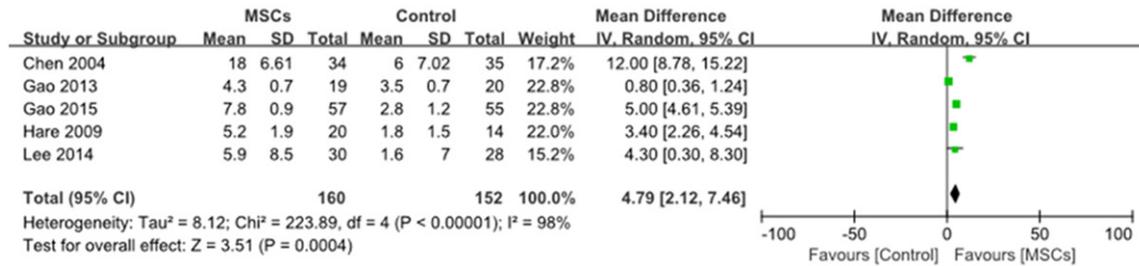
Figure 2. Forest plot of the mean difference (MD, with 95% confidence interval [CI]) in left ventricular ejection fraction (LVEF).
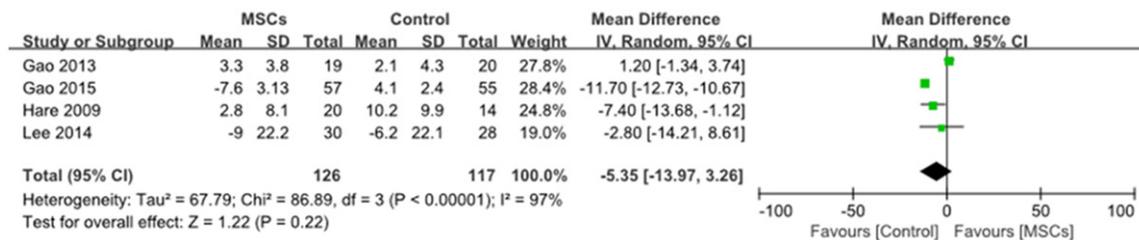
Figure 3. Forest plot of mean difference (MD, with 95% confidence interval [CI]) in left ventricular end-diastolic volume (LVEDV).

bility. Among these, 3 studies using stem cells not derived from MSCs, 2 studies with non-relevant outcomes of heart function, 1 study involving old myocardial infarction, 3 trials duplicated after reading full text carefully and 2 only reported abstract because of ongoing were excluded. Finally, a total of 7 RCTs [16-22] were included in this meta-analysis.

Characteristics of included studies

These 7 RCTs [16-22] included 435 patients of AMI treated with PCI + MSCs in treatment group and PCI + placebo or PCI only in control group. All the studies reported the actual LVEF, LVEDV and LVESV from baseline to follow-up, but only five studies assess the mean changes. We studied the difference in mean changes in LVEF, LVEDV, and LVESV between patients receiving MSCs (n=185) and control treatment (n=172). However, 6 RCTs with patients received MSCs (n=189) and control treatment (n=177) performed safety analysis. All trials applied one of the two types of MSCs, including WJMSCs and BMSCs. 3.08×10^6 to 6×10^9 MSCs were transplanted via the infarct-related artery in 5 studies and via the intravenous route in 2 studies. The sample size in every study was relatively small, ranging from 10 to 58 participants.

Measurements of study outcome included MRI, echocardiography, LV angiography, and SPECT. The follow-up period ranged from 3 to 24 months, four groups included <6 months, 6 months, 12 months and >12 months follow-up data were utilized for the subgroup analysis. Remarkable heterogeneity was observed in each meta-analysis in this study.

Methodological quality assessment of included studies

Overall, the methodological quality of the included trials was good. All pooled studies were RCTs, among which four reported details of the randomization process (**Table 2**), including block randomization [17], sequential number method [18, 19] and sealed envelopes [20]. All four trials using adequate methods concealed treatment allocation. As for blinding of participants and personnel, only three are double blinding trials [17, 18, 20], 2 showed single blind [19] and open-label method [21], the other 2 was not unclear [16, 21]. Among the trials, two did not show details of blinding outcome assessors to treatment allocation [16, 21]. Moreover, at least 89% (ranging from 89 to 100%) of randomized patients were analyzed for the primary outcome in all studies.
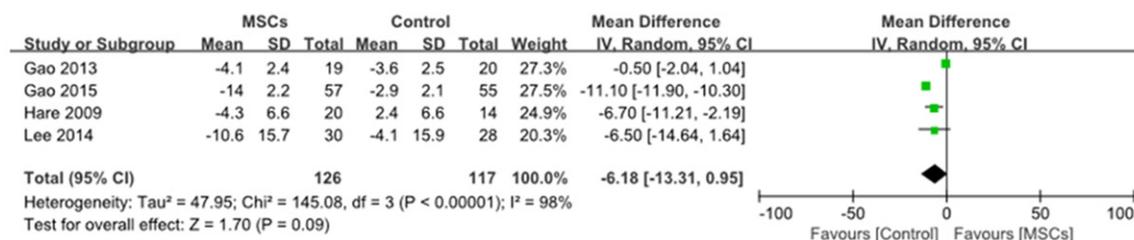
Figure 4. Forest plot of mean difference (MD, with 95% confidence interval [CI]) in left ventricular end-systolic volume (LVESV).
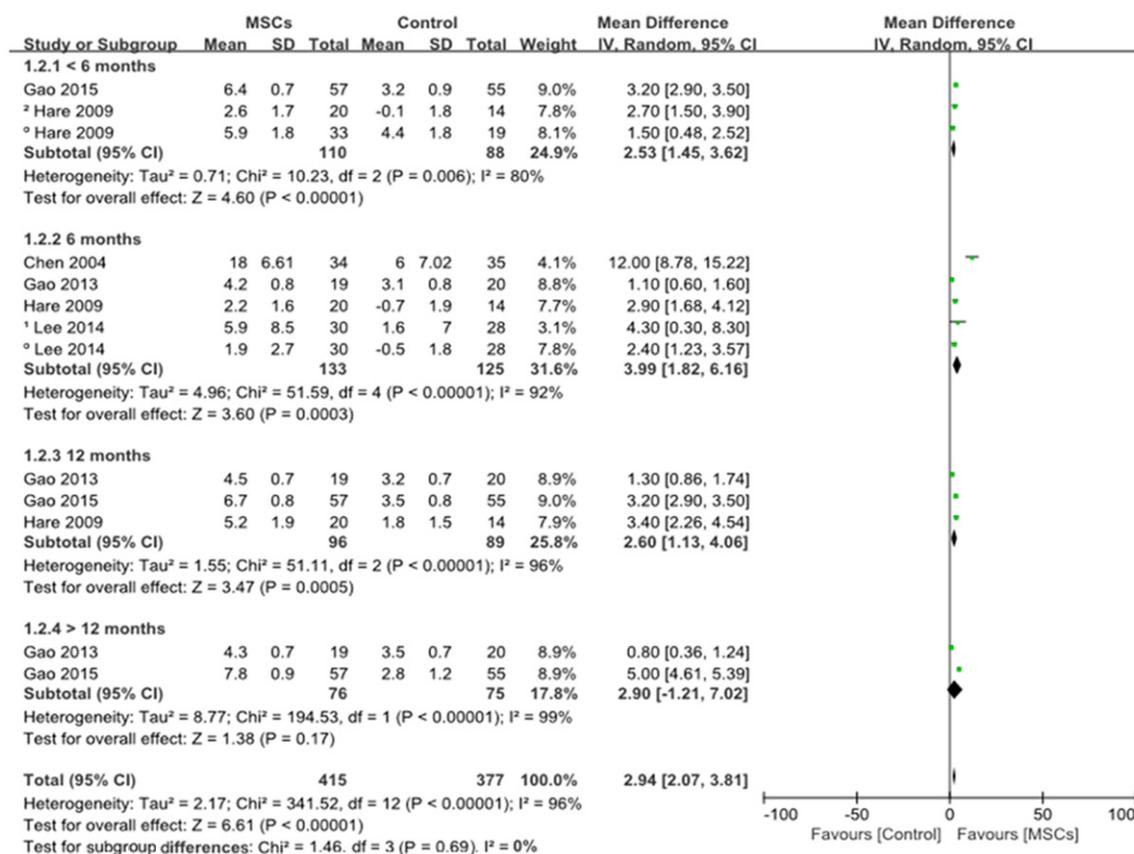

Figure 5. Forest plot of mean difference (MD), with 95% confidence interval [CI] in left ventricular ejection fraction (LVEF) comparing different duration in included trials. Subgroups were divided into <6 months, 6 months, 12 months and >12 months. Numbers represent the different modality used in the same trial: 0, measured with ECHO; 1, measured with SPECT; 2 measured with MRI.

Mean differences in cardiac parameters

Overall, in 5 studies, MSCs therapy led to a significant increase in LVEF by 4.79% (95% CI, 2.12-7.46%, P=0.0004, **Figure 2**). LVEDV decreased by 5.35 ml (95% CI, -13.97-3.26%, P=0.22, **Figure 3**) and LVESV decreased by 6.18 ml (95% CI -13.31 to 0.95, P=0.09, **Figure 4**) were recorded in patients treated with MSCs compared with controls, but both differences were not statistically significant. However, a considerable degree of heterogeneity was observed in the LVEF comparisons (I^2=98%). Planned subgroup analysis regarding duration of follow-up was conducted to further explore possible statistical heterogeneity. We didn't perform sensitivity analysis because of little sample size in each meta-analysis.
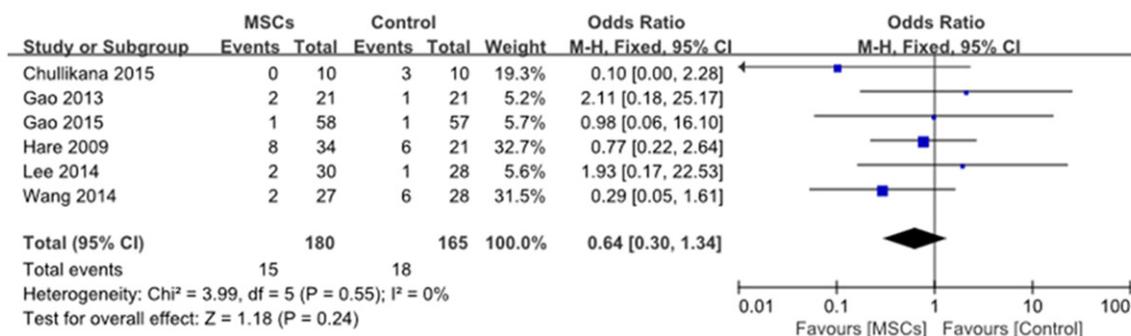
Figure 6. Forest plot of odds ratio (OR, with 95% confidence interval [CI]) in major adverse cardiac events (MACEs).

Table 3. Summary of clinical outcomes

Outcome	Studies reporting	Events/MSCs	Events/Control	OR	95% CI		P-value
MACEs	6	15/180	18/165	0.64	0.30	1.34	0.24
All-cause death	6	2/181	3/165	0.76	0.17	3.50	0.73
Heart failure	2	1/79	1/78	0.99	0.14	7.22	0.99
Instent thrombosis	4	0/119	1/88	0.3	0.01	8.33	0.48
Recurrent MI	4	1/119	1/116	1.00	0.13	7.48	1.00
Rrevascularization	3	1/109	0/106	3.00	0.12	75.19	0.50
Arrhythmia	5	9/153	14/135	0.35	0.07	1.75	0.20
Rehospitalization	4	11/140	11/125	0.61	0.24	1.54	0.29

MSCs, mesenchymal stromal cells; OR, odds ratio; CI, confidence interval; MACEs, major adverse cardiovascular events; MI, myocardial infarction.

Subgroup analysis

The significance of MSCs follow-up period in LVEF was examined. Subgroup analysis revealed that at <6 months of follow-up (n=3 RCTs), LVEF increased by + 2.53% (95% CI, 1.45-3.62; P<0.00001). This beneficial effect was sustained and increased to a more pronounced effect of + 3.99% (95% CI, 1.82-6.16; P= 0.0003) at 6 months (n=5) and + 2.60% (95% CI, 1.13 to 4.06; P=0.0005) at 12 months (n=3) of follow-up, when compared with control. However, this treatment effect disappeared to the + 2.90 (95% CI, -1.21 to 7.02; P=0.17) at long-term follow-up of >12 months, (**Figure 5**). Additionally, different dose of MSCs, type of MSCs, the delivery method, modality of assessment were also identified as possible causes of heterogeneity. We didn't conduct subgroup analysis based on above influence factors because of poor sample size. Sensitivity analysis wasn't performed either because of the same reason.

Relative risks of clinical outcomes

6 studies reported full details on clinical outcomes including MACEs, all-cause death, heart failure, in-stent thrombosis, recurrent myocardial infarction, revascularization, arrhythmia and rehospitalization. MACEs were defined as all-cause death, heart failure, and recurrent myocardial infarction. Overall, MSCs transplantation resulted in a reduction of MACEs (OR 0.64, 95% CI 0.30 to 1.34, I^2=0, P=0.24) (**Figure 6**), compared with controls. There was also a trend toward reduced incidences of all-cause death (OR 0.76, 95% CI 0.17 to 3.50, I^2=0, P=0.73), heart failure (OR 0.99, 95% CI 0.14 to 7.22, I^2=0, P=0.99), in-stent thrombosis (OR 0.30, 95% CI 0.01 to 8.33, I^2 not applicable, P=0.48), arrhythmia (OR 0.35, 95% CI 0.07 to 1.75, I^2=40%, P=0.20) and rehospotalization (OR 0.61, 95% CI 0.24 to 1.54, I^2=0, P=0.29) (**Table 3**), although without statistical significance. A higher incidence of recurrent MI and revascularization was observed (OR 1.00, 3.00, respectively) in MSC-treated patients, albeit not to statistically significant extents. The 95% CI was wide (0.13 to 7.48, 0.12 to 75.19, respectively) that may be primarily due to the limited study population. These results manifested that MSCs therapy is safe for patients with AMI.
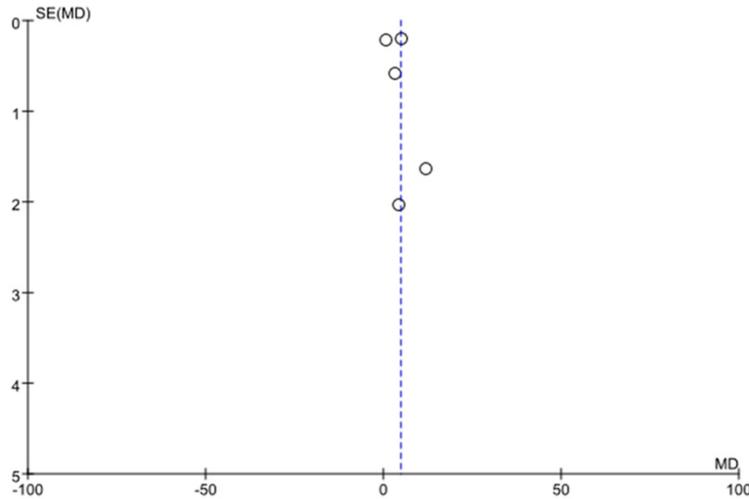
Figure 7. Funnel plot for left ventricular ejection fraction outcome data of the included studies.
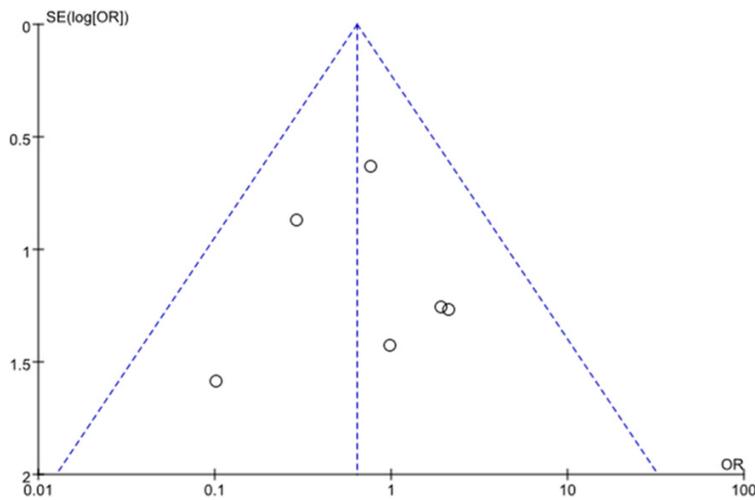
Figure 8. Funnel plot for safety outcome data of the included studies.

Publication bias

Funnel plots of LVEF and MACEs showed that studies were equally distributed around the overall estimate, suggesting that there was no evidence for publication bias (**Figures 7, 8**).

Discussion

This meta-analysis summarized the efficacy and the safety of MSCs administration in patients with AMI after PCI. The results revealed that MSCs therapy may beneficial in improving cardiac function, supporting the utility of this method as a feasible strategy for AMI. Inter-estingly, when subgroup analysis was performed by follow-up duration, this beneficial effect of MSCs therapy on cardiac function disappeared when >12 months. As for safety evaluation, our analysis was unable to detect associations between MSCs treatment and all of the adverse events in patients subjected to MSCs therapy compared with controls. Although a higher incidence of myocardial re-infarction and revascularization was observed, the small sample size included may be a contributory factor. It was a remarkable fact that the CI was wide in our study, which may be explained by relatively small studies and low number of events in all outcomes. Therefore, clinical trials of larger scale and longer-term follow-up should be conducted to fully assess the efficacy and possible adverse effects of MSCs in patients with AMI.

Different stem cells have been used to access the association with coronary artery disease (CAD) in recent years, although the results are controversial. Most studies in patients with CAD have shown a greater increase in LVEF with stem cells than control [23-27]. However, some studies demonstrated discordant results with a decrease in LVEF with treatment or a more robust increase in LVEF in the control group [28-30]. Our meta-analysis got the similar results with most studies. The modest improvement of LVEF was mainly due to a sustained LVEDV and LVESV. The results of subgroup analysis based on follow-up duration showed that MSCs' beneficial impact on LVEF disappeared when >12 months. It was similar to Wollert et al [31] research in which LVEF increased by 6.7% at 6- month in the treatment group but the effect was lost at 18 month. Chen et al [32] also showed initial benefit at 3, 6 and

9 moths of LVEF but that was subsequently lost at 12 month. This may be explained by the dynamic nature of LVEF raising the issue of possible time-limited benefit or discrepancy in the measurements of LVEF when multiple modalities were used for the same patient or the lower number of studies in >12 months group.

We think that our meta-analysis shows strong indications that MSCs therapy is effective in improving LV function for short-term clinical outcome in patients with AMI. Although the number of patients treated with MSCs is still too small, this new cell therapy might prove to be more effective. It is thought that mesenchymal cell populations or cardiac-derived stem cells exhibit more cardioprotective and regenerative potential. As a novel technique, cell-based therapy for CAD has the potential to improve myocardial function and act as adjunctive therapy to medical and reperfusion strategies. In studies of pathological mechanism, administration of BMCs has been shown to regenerate areas of infracted myocardium and coronary capillaries through differentiation into new cardiomyocytes and vascular endothelial cells [33-36]. However, data suggest that the main effect of BMCs may be mediated through their paracrine effects via secretion of cytokines, fibroblast growth factors, and vascular endothelial growth factors that are involved in angiogenesis, inhibition of cardiomyocyte apoptosis, and cell-cell transaction [5, 6, 37, 38]. The result is the replacement of lost myocardial tissue and saving of ischemic and hibernating cardiomyocytes and improvement of LV function.

Cell-base therapy could cause immediate adverse events such as acute infusion toxicity and fever and organ system related adverse events such as cardiovascular, gastrointestinal, renal, pulmonary, neurological, hematological, infection related adverse events, death and malignancy. Our analysis indicated that MSCs were safe in respect of cardiovascular adverse events and death when used in patients with AMI. We didn't perform meta-analysis of other adverse events because of the small size included. We should note that immunomodulatory activities of MSCs could induce acute infusion toxicity, fever and malignancy. Large-scale prospective trials in patients with AMI required to further evaluate the safety for MSCs administration.

Formal testing of publication bias was performed using funnel plots. It was not possible to fully exclude publication bias, although the results showed no statistical significance. There was significant heterogeneity in the efficacy of MSCs administration in our meta-analysis. After subgroup analysis based on duration, heterogeneity remained in every subgroup. This heterogeneity may be linked to multiple factors including cell type, number of injected cells, method of preparation and injection, imaging modality, and patient selection. As we known, sensitivity analysis will access the stability of the combined effect. However, we didn't perform sensitivity analysis because of the small size of RCTs in every subgroup.

Our meta-analysis has several limitations. Firstly, there are two studies published in abstract form only that may influence results despite of our comprehensive search strategy. Secondly, the numbers of patients included are relatively small, which may provide an inaccurate indication of the efficacy and safety of MSCs and precluded the performance of sensitivity analysis. Finally, subgroup analysis did not include factors such as cell therapy timing, cell numbers, cell types, delivery method, or imaging modality due to the limited number of included trials.

Conclusion

This is the first meta-analysis accessing the efficacy and safety of MSCs on cardiac repair in patients with AMI. MSCs transplantation appears to improve left ventricular function and be safe in patients with AMI in short-term. Large randomized double-blinded prospective studies with long-term follow-up are needed to improve the accuracy of the results.

Disclosure of conflict of interest

None.

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