

Meta Analysis

Stem cell transplantation dose in patients with acute myocardial infarction: A meta-analysis

Jia-Ying Xu, Wen-Yuan Cai, Ming Tian, Dai Liu, Rong-Chong Huang*

The Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116000, China

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Abstract

Objective: To evaluate whether stem cell transplantation improves global left ventricular ejection fraction (LVEF) in patients with acute myocardial infarction (AMI), and to determine the appropriate stem cell therapy dose as well as the effective period after stem cell transplantation for therapy.

Methods: A systematic literature search included Pubmed, MEDLINE, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Cochrane Evidence-Based Medicine databases. The retrieval time limit ranged from January 1990 to June 2016. We also obtained full texts through manual retrieval, interlibrary loan and document delivery service, or by contacting the authors directly. According to our inclusion and exclusion criteria, data were extracted independently by two evaluators. In case of disagreement, a joint discussion occurred and a third researcher was utilized. Data were analyzed quantitatively using Revman 5.2. Summary results are presented as the weighted mean difference (WMD) with 95% confidence intervals (CIs). We collected individual trial data and conducted a meta-analysis to compare changes in global left ventricular ejection fraction (Δ LVEF) after stem cell therapy. In this study, four subgroups were based on stem cell dose ($\leq 1 \times 10^7$ cells, $\leq 1 \times 10^8$ cells, $\leq 1 \times 10^9$ cells, and $\leq 1 \times 10^{10}$ cells) and three subgroups were based on follow-up time (<6 months, 6–12 months, and ≥ 12 months).

Results: Thirty-four studies, which included 40 randomized controlled trials, were included in this meta-analysis, and 1927 patients were evaluated. Changes in global LVEF were significantly higher in the stem cell transplantation group than in the control group (95% CI: 2.35–4.26%, $P < 0.01$). We found no significant differences in Δ LVEF between the bone marrow stem cells (BMCs) group and control group when the dose of BMCs was $\leq 1 \times 10^7$ [Δ LVEF 95% CI: 0.12–3.96%, $P = 0.04$]. The Δ LVEF in the BMCs groups was significantly higher than in the control groups when the dose of BMCs was $\leq 1 \times 10^8$ [Δ LVEF 95% CI: 0.95–4.25%, $P = 0.002$] and $\leq 1 \times 10^9$ [Δ LVEF 95% CI: 2.31–4.20%, $P < 0.01$]. In addition, when the dose of BMCs was between 10^9 and 10^{10} cells, we did not observe any significant differences [Δ LVEF 95% CI: -0.99 –11.82%, $P = 0.10$]. Our data suggest stem cell therapy improves cardiac function in AMI patients when treated with an appropriate dose of BMCs.

* Corresponding author.

E-mail address: rchuang@dlmedu.edu.cn (R.-C. Huang).

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Conclusion: Stem cell transplantation after AMI could improve global LVEF. Stem cells may be effectively administered to patients with AMI doses between 10^8 and 10^9 cells.

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Keywords: Stem cell; Acute myocardial infarction; Left ventricular ejection fraction; Cell dosage

Introduction

Coronary heart disease is the number one cause of death in China. Acute myocardial infarction (AMI) is an important factor that predicts increased mortality and heart failure incidence. Although modern therapeutics such as optimal drug treatment, percutaneous coronary intervention (PCI), and coronary artery bypass lower patient mortality and improve long-term prognosis, infarcted cells cannot be recovered. As a result, myocardial remodeling ensues and results in heart failure. Therefore, recent studies regarding the treatment of myocardial infarction have focused on how to repair infarcted cells and reduce myocardial remodeling to improve post-infarction heart function.

It has been demonstrated that stem cell transplantation can significantly improve post-AMI systolic and diastolic function, as well as decrease the severity of necrocytosis and apoptosis in animal hearts, thereby resulting in decreased mortality in experimental animals.¹ Moreover, clinical studies have found that stem cell transplantation can improve post-infarction left ventricular systolic and diastolic function.^{2,3} However, other studies have found that AMI patients did not benefit from stem cell transplantation.^{4,5} Therefore, studies are currently evaluating efficacy issues in stem cell transplantation using different types of cells, different routes of transplantation, increased cell doses, and the frequency of transfer.^{2,6,7} Nonetheless, few reports have examined the optimal dose of transferred cells that should be used.^{8,9} The present meta-analysis was designed to investigate the impact of various doses of stem cells on the heart function of AMI patients to determine the optimal dose that should be used in patients with AMI.

Materials and methods

Source of data and search strategy

We searched the electronic databases including PubMed, MEDLINE, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Cochrane Evidence-based

medicine databases using acute myocardial infarction (AMI), stem cell, mononuclear stem cell, and percutaneous coronary intervention (PCI) as keywords. We evaluated studies published from January 1990 to June 2016. We did not limit the language of the publication. Alternatives included manual retrieval, interlibrary loan, document delivery service, or contacting the author directly.

Inclusion and exclusion criteria

We employed the following inclusion criteria: (1) Randomized controlled trials (RCTs) with follow-up times ≥ 3 months; (2) Patients clinically diagnosed with AMI. The experimental group received both percutaneous coronary intervention and autologous bone marrow stem cells whereas the control group was prescribed a standard medication regime; (3) Patients in the experimental group received autologous bone marrow stem cells via coronary arteries with no limit to cell types or doses; (4) The outcome variable was left ventricular ejection fraction (LVEF); (5) Chinese or English publication language.

Exclusion criteria were the following: (1) Intravenous or intramyocardial injection as the routes of stem cell delivery; (2) Trials with no control group; (3) Incomplete data (or no data) regarding stem cell dose; or (4) Repeated studies on the same subjects.

Data extraction

All references were evaluated by two authors according to the inclusion/exclusion criteria. Data were extracted according to tables designed beforehand and cross-checked. Disagreements were resolved by discussion between the authors and decided by a third investigator, if necessary.

Statistical methods

We used the Revman 5.2 software package (The Cochrane Collaboration, Copenhagen, Denmark) to perform statistical analyses. Categorical data are presented as odds ratios with 95% confidence intervals

(CIs). Quantitative data are presented as weighted mean differences (WMD) with 95% CIs. Subgroup analyses were performed according to possible causative factors of clinical heterogeneity, such as various stem cell doses. Heterogeneity was examined using Q tests and I^2 statistic. $P < 0.1$ was regarded as positive heterogeneity. I^2 values between 0% and 40% were regarded as unimportant heterogeneity, 30–60% as moderate heterogeneity, 50–90% as significant heterogeneity, and 75–100% as massive heterogeneity. Homogeneous and heterogeneous data were analyzed using the fixed effect and random effect models, respectively.

Results

Literature search results

As shown in Fig. 1, 2505 articles were found using computerized methods and an additional 102 were identified by manual retrieval and interlibrary loan. Of the 2607 total articles, 2260 were repetitive and therefore excluded. The titles and abstracts of the remaining 347 articles were read, and another 264 articles were excluded. After reading the complete texts,

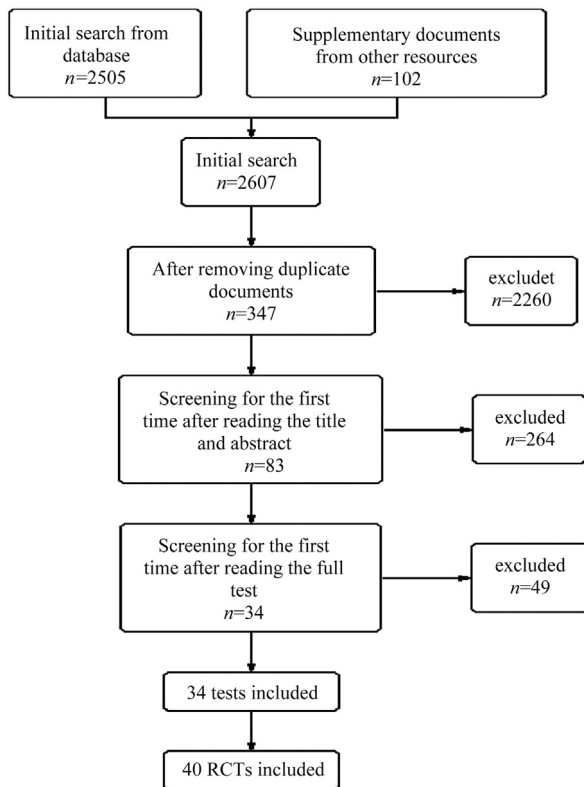


Fig. 1. Flow diagram to illustrate the data collection and screening processes. RCT: randomized controlled trials.

49 articles did not meet the inclusion criteria and were excluded. Ultimately, 34 articles containing 40 RCTs were selected.

Material selection

We identified 40 RCTs.^{2–7,10–38} Our research variables were differences in LVEF (Δ LVEF) before and after follow-up in both the experimental and control groups. Our meta-analysis included a total of 1927 patients (1037 in the experimental groups and 890 in the control groups). Patient characteristics are shown in Table 1.

Heterogeneity analyses

Heterogeneity was examined using I^2 tests. With an overall $I^2 > 50\%$ in our study, heterogeneity existed among the studies. A random effects model was used for further analyses. In subgroup analyses, the subgroup with a stem cell dose $\leq 1 \times 10^7$ had an I^2 value of 0%; therefore, a fixed effect model was used. The heterogeneity in other subgroup analyses (including different doses and follow-up durations) was 0, indicating the population was non-heterogeneous.

Evaluation of Δ LVEF

Weighted-mean differences between pre- and post-follow-ups were used as a summary statistic. Δ LVEF in the experimental group was 3.31% (95% CI: 2.35–4.26%, $P < 0.01$), which was higher than that in control group (Fig. 2). This result suggests that stem cell therapy may enhance the effect on LVEF based on basic treatment in AMI patients.

The impact of different Δ LVEF doses in AMI patients

Table 2 shows that the 40 RCTs were divided into four groups (stem cell doses $\leq 1 \times 10^7$, $\leq 1 \times 10^8$, $\leq 1 \times 10^9$, and $\leq 1 \times 10^{10}$). Analyses of the correlation between stem cell dose and changes in LVEF before and after stem cell transplantation showed that AMI patients who received stem cell therapy had higher Δ LVEF values than control patients. The differences were 2.04% (95% CI: 0.12–3.96%, $P = 0.04$), 2.60% (95% CI: 0.95–4.25%, $P = 0.002$), 3.25% (95% CI: 2.31–4.20%, $P < 0.01$), and 5.41% (95% CI: -0.99 –11.82%, $P = 0.10$), respectively (Fig. 2). Therefore, our data indicate significant LVEF improvement in AMI patients who received stem cell therapy at a dose of 10^8 – 10^9 cells.

Table 1
The basic characteristics of included studies.

Investigator group	Patients (stem cell/control)	Change of LVEF (%) and 95% CI		Dose of stem cell	Time of stem cell administration, d	Follow-up time, month	Selection of stem cell	Prepare of stem cell administration
		Experimental	Control					
Chen (2004)	34/35	18 (4.74)	6 (5.59)	8×10^9	18.4	6	BMSC	DGS
Assmus (2002)	19/11	8.5 (6.44)	2.5 (6.37)	7.35×10^6	4.3	4	Not given	DGS
Manginas (2007)	12/12	2.5 (4.95)	-3.6 (5.59)	$2-16 \times 10^6$	Not given	13	BMMC	DGS
Hirsch (2010)	67/60	3.8 (7.4)	4 (5.8)	$2.9 \pm 1.6 \times 10^8$	3-8	4	BMMC	DGS
Janssens (2006)	30/30	3.4 (6.9)	2.2 (7.3)	$1.7 \pm 0.7 \times 10^8$	1	4	BMSC	DGS
Kang (2006)	25/25	5.1 (9.1)	-0.2 (8.6)	$1-2 \times 10^9$	3	6	PBSCs	Spectrum acquisition
Meyer (2006)	30/30	6.7 (6.5)	0.7 (8.1)	$2.4 \pm 0.9 \times 10^9$	4.8	6	BMMC	DGS
Quyumi-HD (2011)	2/10	0.2 (0.8)	1 (7.8)	$1.4 \pm 0.2 \times 10^7$	8.3	6	BMMC	DGS
Quyumi-LD (2011)	4/10	-0.02 (13)	1 (7.8)	$4.8 \pm 0.6 \times 10^6$	8.3	6	BMMC	DGS
Quyumi-MD (2011)	5/10	6.7 (4)	1 (7.8)	$9.9 \pm 0.7 \times 10^6$	8.3	6	BMMC	DGS
Roman (2015)	26/24	6 (6)	4 (7)	$6 (3.1-6.5) \times 10^7$	3-5	12	BMMC	DGS
Roncalli (2010)	47/44	1.9 (6.89)	2.2 (6.87)	1×10^8	9	3	Not given	Unknown
Tendera-S (2009)	51/20	4.2 (14.5)	0.5 (9.08)	1.9×10^6	7	6	BMMC	DGS
Tendera-U (2009)	46/20	4.4 (10.92)	0.5 (9.08)	1.78×10^8	7	6	BMMC	DGS
Traverse (2010)	30/10	6.2 (9.8)	9.4 (10)	1×10^8	3-10	6	BMMC	DGS
Wohrle (2010)	29/13	5.7 (8.4)	1.8 (5.3)	$3.81 \pm 1.3 \times 10^8$	5-7	6	BMMC	DGS
Yao-DD (2009)	15/12	7.3 (3.43)	2.1 (1.71)	$2.0 \pm 1.4 \times 10^8$	3-7	3	BMMC	DGS
Yao-SD (2009)	12/12	5.2 (2.72)	2.1 (1.71)	$1.9 \pm 1.2 \times 10^8$	3-7	3	BMMC	DGS
Huang (2006)	20/20	3.3 (2.92)	1.2 (2.16)	$1.8 \pm 4.2 \times 10^8$	0.08	6	BMMC	DGS
Huikun (2008)	36/36	7.1 (12.3)	1.2 (11.5)	$4.0 \pm 2.0 \times 10^8$	3	6	BMMC	DGS
Schachinger (2006)	27/27	3.2 (6.8)	0.8 (6.8)	$2.4 \pm 1.7 \times 10^8$	3-6	4	BMMC	DGS
Suarezdelzo (2007)	10/10	20 (8)	6 (10)	9×10^8	7	3	BMMC	DGS
Sürder LD (2016)	42/55	-0.7 (10.11)	-1.9 (9.84)	1.395×10^8	24	12	BMMC	DGS
Sürder SD (2016)	53/55	-0.9 (10.50)	-1.9 (9.84)	1.597×10^8	6	12	BMMC	DGS
Cao (2008)	41/45	8.17 (2.33)	5.41 (2.43)	$1.25-5.0 \times 10^8$	7	6	BMMC	DGS
Meluzin-HD (2008)	22/22	5 (4.69)	2 (4.69)	$0.9-2.0 \times 10^8$	6.8	6	BMMC	DGS
Meluzin-LD (2008)	22/22	3 (4.69)	2 (4.69)	$0.9-2.0 \times 10^7$	8.9	6	BMMC	DGS
Ge (2006)	10/10	4.8 (6.76)	-1.9 (4.14)	4×10^7	0.62	6	BMMC	DGS
Huang (2007)	20/20	7.1 (3)	2.9 (2.6)	$1.2 \pm 6.5 \times 10^8$	1	6	BMMC	DGS
Jin (2008)	14/12	4.28 (3.53)	0.28 (4.03)	$6.3 \pm 1.6 \times 10^7$	7-10	6	BMMC	DGS
Karpov (2005)	16/10	6.3 (7.31)	4.9 (3.85)	$8.8 \pm 4.9 \times 10^7$	7-21	6	BMMC	DGS
Li (2007)	35/23	7.1 (5.66)	1.6 (4.95)	$7.2 \pm 7.3 \times 10^7$	5	6	BMMC	DGS
Lunde (2006)	50/50	3.1 (7.9)	2.1 (9.2)	$0.68 (0.5-1.3) \times 10^8$	4-8	6	BMMC	DGS
Penicka (2007)	14/10	6 (5.41)	8 (4.03)	2.64×10^9	4-11	4	BMMC	DGS
Piepoli (2010)	17/15	12 (5.28)	6.7 (6.44)	2.49×10^8	4	12	Not given	Unknown
Plewka (2009)	38/18	9 (6.1)	5 (4.95)	$1.44 \pm 0.49 \times 10^8$	7	6	Not given	DGS
You (2008)	7/16	13.3 (3.98)	4 (3.58)	7.5×10^7	14	2	BMSC	DGS
Grajek (2010)	31/14	2.74 (7.07)	-0.11 (6.47)	$4.1 \pm 1.8 \times 10^8$	4-6	6	Not given	DGS
Nogueira-AG (2009)	14/6	5.5 (7.22)	0.48 (11.3)	1×10^8	5.5	6	BMMC	DGS
Nogueira-VG (2009)	14/6	0.39 (6.39)	0.48 (11.3)	1×10^8	6	6	BMMC	DGS

Data of dose of SC and time of SC administration are a separate number, range or mean±SD, depending on original data of the articles.

BMSC: bone marrow stem cell; BMMC: bone marrow mononuclear cell; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; HD: high dose; MD: medium dose; LD: means low dose; S: selected BMSC; U: unselected BMSC; DD: double BMSC dose (first delivery: mean 2.0 (SE 1.4) × 10⁸, second delivery: mean 2.1 (SE 1.7) × 10⁸); SD: single BMSC dose (dose of stem cells: mean 1.9 (SE 1.2) × 10⁸); AG: coronary artery route BMSC; VG: coronary venous route BMSC; DGS: density gradient separation.

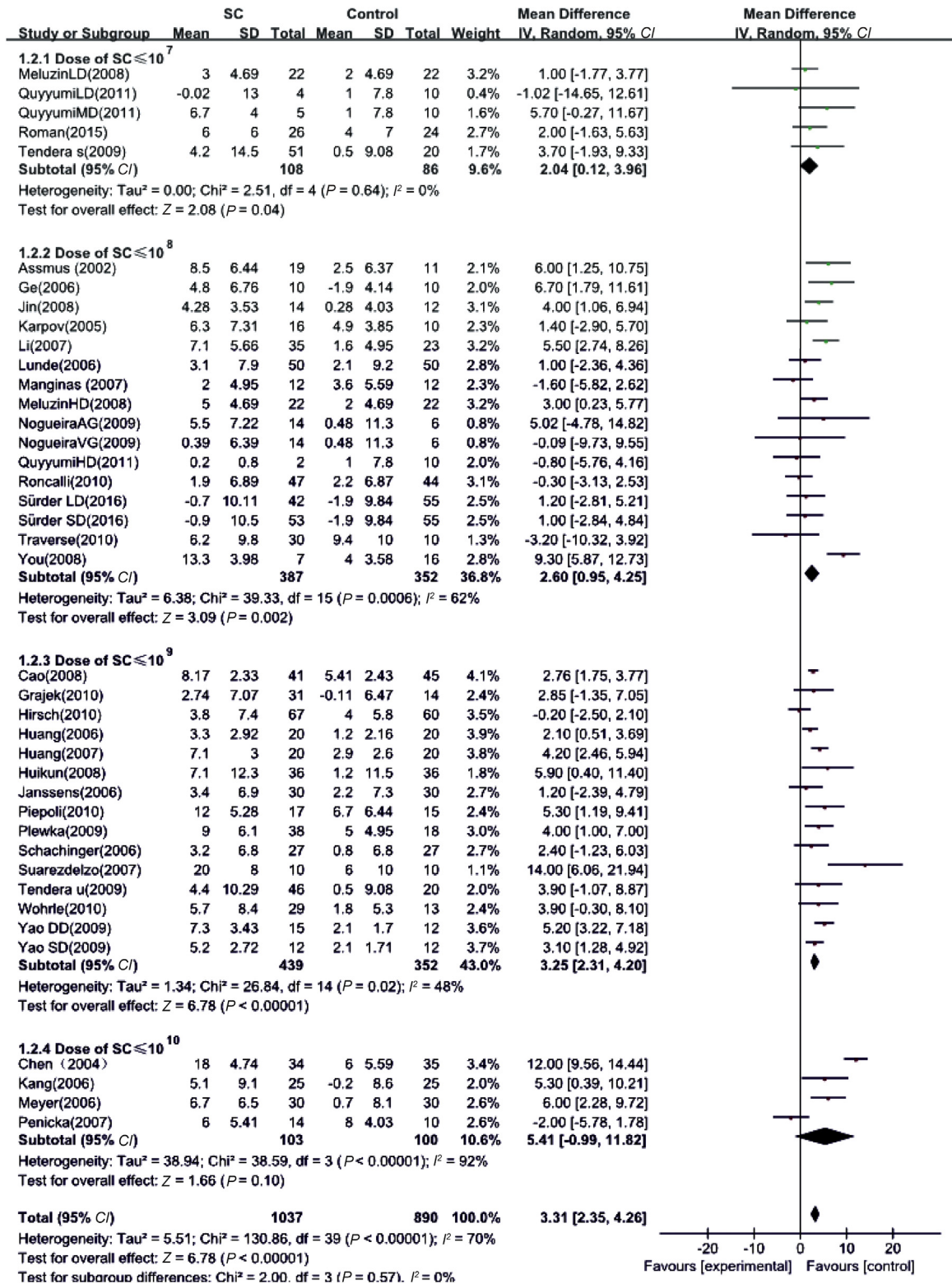


Fig. 2. Effects of stem cell dosage on LVEF. SD: standard deviation; SC: stem cell.

Table 2
Number of patients and studies in groups of different stem cell doses.

Dose of stem cell	Number of study, <i>n</i>	Number of patients (stem cell/control)
$\leq 1 \times 10^7$	5	108/86
$\leq 1 \times 10^8$	16	387/352
$\leq 1 \times 10^9$	15	439/352
$\leq 1 \times 10^{10}$	4	103/100

Mortality data

Eleven studies reported deaths cases, in experimental group, there were 13 death cases in total, 6 patients in control group (Table 3). The results showed no significant statistical differences between the experimental group and the control group (95% CI: 0.60–2.87%, $P = 0.50$) (Fig. 4).

Table 3
The mortality of included studies.

Investigator group	Number of patients (stem cell/control)	Number of death (stem cell/control)	Mortality (%)	
			Experimental	Control
Chen (2004)	34/35	0	0	0
Assmus (2002)	19/11	0	0	0
Manginas (2007)	12/12	0	0	0
Hirsch (2010)	67/60	0	0	0
Janssens (2006)	30/30	1/0	3.23	0
Kang (2006)	25/25	0/1	0	0
Meyer (2006)	30/30	0	0	0
Quyyumi-HD (2011)	2/10	0	0	0
Quyyumi-LD (2011)	4/10	0	0	2.78
Quyyumi-MD (2011)	5/10	0	3.33	0
Roman (2015)	26/24	0	0	0
Roncalli (2010)	47/44	1/0	0	4.00
Tendera-S (2009)	51/20	1/0	0	1/0
Tendera-U (2009)	46/20	1/0	0	0
Traverse (2010)	30/10	0	0	0
Wohrle (2010)	29/13	0	0	0
Yao-DD (2009)	15/12	0	0	0
Yao-SD (2009)	12/12	0	0	0
Huang (2006)	20/20	0	0	0
Huikun (2008)	36/36	0/1	0	0
Schachinger (2006)	27/27	2/2	0	0
Suarezdelzo (2007)	10/10	0	0	0
Sürder LD (2016)	42/55	1/0	0	0
Sürder SD (2016)	53/55	3/0	5.26	11.11
Cao (2008)	41/45	0	0	0
Meluzin-HD (2008)	22/22	0	0	0
Meluzin-LD (2008)	22/22	0	0	0
Ge (2006)	10/10	0	0	0
Huang (2007)	20/20	0	2.13	0
Jin (2008)	14/12	0	7.41	7.41
Karpov (2005)	16/10	0	0	0
Li (2007)	35/23	0	2.38	0
Lunde (2006)	50/50	0	5.66	0
Penicka (2007)	14/10	0	1.96	0
Piepoli (2010)	17/15	0	2.17	0
Plewka (2009)	38/18	2/2	0	0
You (2008)	7/16	0	0	0
Grajek (2010)	31/14	1/0	0	0
Nogueira-AG (2009)	14/6	0	0	0
Nogueira-VG (2009)	14/6	0	0	0

Note: BMSC: bone marrow stem cell; HD: high dose; MD: medium dose; LD: low dose; S: selected BMSC; U: unselected BMSC; DD: double BMSC dose (first delivery: mean 2.0 (SE 1.4) $\times 10^8$, second delivery: mean 2.1 (SE 1.7) $\times 10^8$); SD: single BMSC dose (dose of stem cells: mean 1.9 (SE 1.2) $\times 10^8$); AG: coronary artery route BMSC; VG: coronary venous route BMSC.

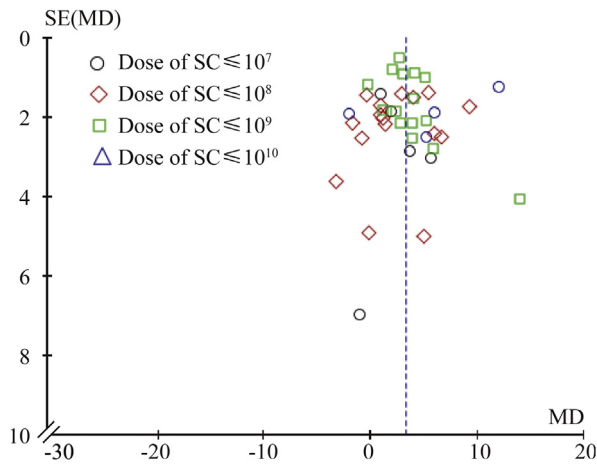


Fig. 3. Funnel plot of publication bias. SC: stem cell; MD: medium dose.

Publication bias evaluation

In our study, we examined publication bias using a funnel plot. We found symmetrical distribution of the included studies, suggesting acceptable publication bias in the studies used in our meta-analysis (Fig. 3).

Discussion

Our study found improved LVEF in AMI patients after stem cell therapy using a dose of 10^8 – 10^9 cells. Stem cell therapy has been used in the treatment of hematological malignances for more than 40 years.³⁹ Multiple RCTs have assessed its safety and efficacy in heart disease^{2,12,14,16,22,37} and reported that bone marrow-derived stem cell transplantation may improve

heart function without increasing the incidence of adverse cardiac events in AMI patients.⁴⁰ However, compared with the 40% improvement in LVEF in animal experiments,¹ there is a lack of large-scale, long-term, multi-center RCT data confirming these results. Indeed, in several clinical studies, LVEF improvement after autologous bone marrow-derived stem cells was minimal and inconsistent. These results are likely attributed to different types of subjects, methods of bone marrow stem cell separation, transplanted stem cell doses, timing of transplantation, and evaluation methods.^{40,41} Bone marrow samples were collected under sterile conditions from the iliac crest in local anesthesia. The cell processing in most studies was density gradient centrifugation. Moreover, few studies have evaluated the relationship between cell dose and LVEF. By analyzing the relationship between cell dose and Δ LVEF, we found that as cell dose increases, LVEF improves. In patients that received cell doses $\leq 1 \times 10^7$, although the differences were not significant, there was a trend toward improved LVEF. Of the 40 included studies, 31 involved cell doses between 10^8 and 10^9 . Results from these studies showed higher Δ LVEF values in the cell transplantation groups compared to control subjects. Using higher cell doses ($\leq 1 \times 10^{10}$), Δ LVEF was higher in the experimental groups than control groups, although the difference was not statistically significant. If not acquired from *in vitro* cultivation and amplification, large doses of stem cells indicate a large amount of blood or bone marrow is drawn from AMI patients themselves. Therefore, it is often hard to secure such high doses of stem cells and only four studies (including 103 experimental patients and 100 control patients) using this dose range were included in this meta-analysis.

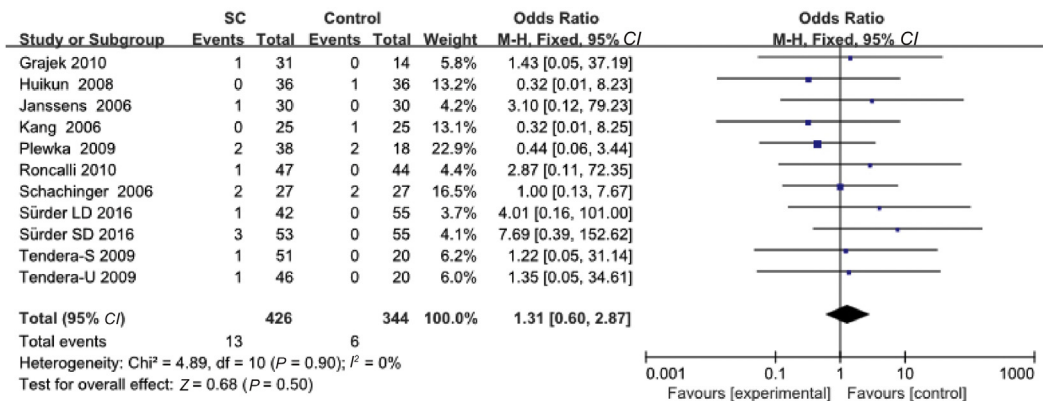


Fig. 4. Mortality of stem cell transplantation.

LD: means low dose; S: selected bone marrow stem cell; U: unselected bone marrow stem cell; SD: single BMSC dose (dose of stem cells: mean 1.9 (SE 1.2) $\times 10^8$).

This small sample size may increase sampling error and lead to bias in the final results.⁴² Other studies have shown that Δ LVEF is 12.00% (95% CI: 9.56–14.44%) higher in the stem cell group.² However, these results may be related to bone marrow mesenchymal stem cells, which was transplanted in this study. However, the source of stem cells is bone marrow mononuclear cells in other studies.⁴³

Because the majority of studies in this meta-analysis used cell doses of 10^8 – 10^9 , we further studied the short- and long-term impact of stem cells in this dose range on the hearts of AMI patients. Most studies lacked long-term consecutive data analyses on patients. Most studies had follow-up periods less than 3 years. Most studies considered short-term (~6 months) stem cell therapy effective; however, in long-term evaluations, the data are inconsistent regarding whether cell transplantation improved heart function. Currently, few follow-up studies have evaluated patients 18 months to 3 years after cell transplantation. Because it is impossible to objectively evaluate these results, more studies are warranted.

Many factors may have affected our meta-analysis results. First, LVEF is a major variable to evaluate the effect of stem cell therapy, and the methods were not identical. Different methodologies for evaluating heart function may have altered the results. Due to the small sample size, our study was unable to investigate the relationship between different heart function evaluation methods and transplanted cell doses. As more RCTs are published, future meta-analyses can be grouped according to evaluation method and subgroup analyses can be conducted to achieve more reliable results. Moreover, although the majority of included studies showed benefits from stem cell therapy, nine studies suggested no benefits or reported worse outcomes for transplanted patients than controls.^{4,5,10,15,27,30} However, these data may be attributed to the small sample size, which results in large sampling errors and may alter the study results.⁴²

Second, Δ LVEF is not the only variable used to evaluate heart function. Key factors involved in ventricular remodeling and heart dysfunction include myocardial necrosis and the absolute decrease in cardiomyocyte number caused by myocardial ischemia and reperfusion injury. Many studies, in addition to Δ LVEF, also included left ventricular end diastolic volume (LVEDV).^{17,18,25} However, there were insufficient LVEDV data to analyze statistically.

Third, the mortality data and report it either numerically or in table format. Mortality data is absent also important at the moment. Ventricular function is

essential, but the change in mortality is crucially more significant parameter, that also reveals any possible adverse effect from cell transplantation. Such data is usually poorly presented in these RCTs. Our study found that the stem cells transplantation had not too much influence on mortality.

Finally, the timing of transplantation may affect the results. Some studies have confirmed that the timing of stem cell introduction affects AMI patients. Immediately after AMI (1–2 days), presumably due to significant myocardial ischemia and inflammation, post-reperfusion oxygen burst, and severe peroxidation injury, there is increased local apoptosis of transplanted stem cells. Thus, the efficacy of stem cell therapy is poor early after AMI. Six to nine days after AMI, debris in the heart is liquefied and absorbed. This process may also influence survival of the surrounding infarct areas and adversely affect transplanted stem cell survival and differentiation. The microenvironment differs in various pathological stages and may affect transplanted stem cell survival and differentiation. In clinical trials, the timing of cell transplantation leads to different results. During chronic and stable stages, the pathological environment differs from the acute state and provides conditions for transplanted stem cell growth and differentiation. Therefore, most studies recommend transplantation 2–9 days after AMI.⁴⁴ The earliest transplantation noted in our meta-analysis was 2 hours after AMI and the longest transplantation was 24 days after AMI. Therefore, this large time span may affect the results of our study.

Although all included studies were RCTs, the total sample size remained small, thereby resulting in an inevitable bias in summary statistics. Thus, more RCTs that focus on transplanted cell dose are warranted to investigate the optimal stem cell dose for transplantation.

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