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REVIEW

Therapeutic effect of mesenchymal stem cell therapy in the LVEF, LVEDV, and LVESV after myocardial infarction

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ABSTRACT

OBJECTIVES: The present study was aimed to investigate the therapeutic effect of mesenchymal Stem Cell Therapy in the left ventricular ejection fraction (LVEF), left ventricular enddiastolic volume (LVEDV), and left ventricular endsystolic volume (LVESV) after myocardial infarction (MI).

BACKGROUND: Previous investigations propose that stem cell therapy may help treat myocardial infarction (MI). However, there are controversial data from different studies.

METHODS: We studied the relevant scientific literature available up to 2020. Comprehensive Meta-Analysis Software (CMAS) Version 2.0 were used for statistical analyses. Fixed or random-effect model was used to identify the weighted mean difference (WMD) with 95% confidence intervals (CI). The statistically significant level used for interpreting publication bias was less than 0.05.

RESULTS: We identified 30 studies that met the inclusion criteria. In the overall pooled estimate, cell therapy had an effect on the LVEF change from baseline to follow-up (WMD: 2.98 mL, 95% CI: 1.66 to 4.29). The pooled WMD was found to be –4.16 (95% CI: –7.91 to –0.40) and –5.62 (95% CI: –9.20 to –2.00), for LVEDV, and LVESV, respectively. Thus, reduction in LVEDV and LVESV were significant in the treatment group participants.

CONCLUSIONS: The present systematic review indicated that cell therapy in patients, who have MI could be effective and applicable clinically *(Tab. 3, Fig. 7, Ref. 48).* Text in PDF *www.elis.sk*

KEY WORDS: myocardial infarction, stem cell, systematic review, randomized clinical trials.

Introduction

Heart disease is still one of the main universal reasons of death and according to evidence it will increase in further years (1). It was estimated that 2.8 fold increase in death number due to heart disease would occur from 2000 to 2050 (2). The major problem in the people, who suffer from heart disease, is functional impairment, which is caused by ischemic failure (3). The key management of ischemic heart disease (IHD), which manifests clinically as MI and ischemic cardiomyopathy, is the effective integration of pharmacological therapy combined with modern reperfusion strategies that has improved the patients' long-term prognosis and raised their life expectancy (1). Although these current therapies declined the mortality rate after an acute MI, they were unable to recover infracted areas so the existence of damaged cardiomyocytes remains as an important risk factor for further progression to heart failure (4). Thus, triggering cardiomyocytes regeneration in damaged tissue could be the best way to recover the heart function and increase the affected people survival rate. In recent years, several investigations worked on myocardial regeneration through stem/progenitor cell transplantation therapy (5). Five kinds of stem cells containing bone marrow-derived stem cells (BMSCs) (6, 7) or bone marrow-derived mononuclear stem cells (BMMNCs), mesenchymal stem cells (MSC) (8), cardiac stem cells (CSCs), cardiosphere-derived stem cells (CDCs), and embryonic stem cells (ESCs) have mostly been studied for cardiomyocyte regeneration. The preclinical studies and some clinical studies suggested that stem cell therapy had a satisfactory effect on the performance of the cardiac function after heart failure (5). To determine the efficacy of novel treatments in heart failure, scientists usually measure important markers related to left ventricle because this chamber is in charge of pushing the blood into all the body and the existence of any failure on it could cause a variety of disabilities in the patient. Thus, most of clinical trials with the aim of assessing the efficiency of stem cells were

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Tab. S1. Search strategy for the PubMed/Medline database.

Search	Query
#3	((((((((((((((Myocardial Infarction(MeSH Terms)) OR (Myocardial Infarction(Title/Abstract))) OR (myocardial failure(Title/Abstract))) OR (Myocardial Ischemia(Title/Abstract)))) OR (cardiomyopathy(Title/Abstract))) OR (myocardiopathy(Title/Abstract))) OR (Cardiovascular Stroke(Title/Abstract))) OR (Myocardial Infarct(Title/Abstract))) OR (Heart Attack(Title/Abstract))) OR (cardiac failure(Title/Abstract))) OR (heart failure(Title/Abstract)) AND ((((((Stem Cells(MeSH Terms)) OR (Stem Cells(Title/Abstract))) OR (mesenchymal stem cell(Title/Abstract))) OR (mesenchymal stromal cell(Title/Abstract))) OR (mesenchymal progenitor cell(Title/Abstract))) OR (Mesenchymal Stem Cells(MeSH Terms))
#2	((((((((((((((Myocardial Infarction(MeSH Terms)) OR (Myocardial Infarction(Title/Abstract))) OR (myocardial failure(Title/Abstract))) OR (Myocardial Ischemia(Title/Abstract)))) OR (cardiomyopathy(Title/Abstract))) OR (myocardiopathy(Title/Abstract))) OR (Cardiovascular Stroke(Title/Abstract))) OR (Myocardial Infarct(Title/Abstract))) OR (Heart Attack(Title/Abstract))) OR (cardiac failure(Title/Abstract))) OR (heart failure(Title/Abstract))
#1	(((((Stem Cells(MeSH Terms)) OR (Stem Cells(Title/Abstract))) OR (mesenchymal stem cell(Title/Abstract))) OR (mesenchymal stromal cell(Title/Abstract))) OR (mesenchymal progenitor cell(Title/Abstract))) OR (Mesenchymal Stem Cells(MeSH Terms))

investigated on left ventricular (LV) remodeling after treatment. In this way, watching on three measurable values, including left ventricular ejection fraction (LVEF), left ventricular end-systolic volumes (LVESV) from the baseline, and left ventricular end-diastolic volume (LVEDV) are more important (9–11). Whereas LVEF is an important marker to identify the extent of ventricles abnormalities after a heart disease, it is considered as a guide to estimate the risk of morbidity rate and also the treatment efficacy (9). As well, it has been demonstrated that measuring the LVESV could be the key marker to estimate the patient survival after MI (10). Another important factor that serves as a measurable value to demonstrate how well is the heart performing, is LVEDV (11). So, evaluating these three markers will provide a vision for scientists to find the outcome of novel treatment. Although preclinical and clinical research suggested that stem cell therapy has been safe and useful, there were some reports, which propound the idea that stem cell therapy are unable to treat the heart failure effectively. Thus, current study aimed to review the studies to evaluate the useful effects of stem cell therapy after MI through a comprehensive systematic review and meta-analysis.

Material and methods

This study is in fulfilment of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement (12).

Search strategy and selection criteria

We investigated the PubMed/Medline, EMBASE, Cochrane Library, Scopus, google scholar and reference lists of relevant articles from January 1, 2000 to January 1, 2020. The following keywords were used: myocardial infarction, myocardial failure, stem cells, and mesenchymal stem cell. The search was restricted to English articles. Details of strategies used in PubMed/Medline are given in the Table S1 in Supplement. Only randomized controlled trials (RCT) studies, in which stem cells were used as a treatment for MI, were included. RCTs with the following criteria were included: (1) the intervention involved any stem cells without a limitation by administration route or dose, (2) at least three months' follow-up period, and (3) in the control arm patients did not receive stem cells. Review articles, duplicate publications, and articles with unclear data were ruled out from the analysis.

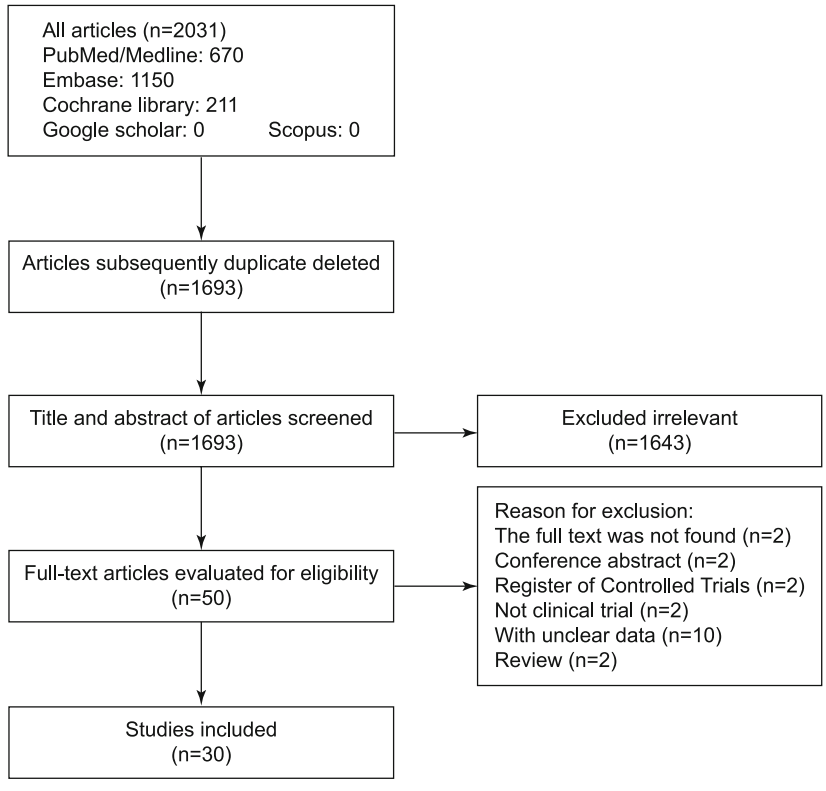

Fig. 1. Diagram of study selection for the inclusion in this research.

Tab. 1. Features of the involved studies.

First author	Published year	Country	Study design	Mean Age (yrs.)	Total No. of Patients Enrolled	Follow-up (mo.)	Time from PCI and/or MI to transplantation	Cell type
Laguna (15)	2018	Spain	RCT	62.63	20	9	10-15 days	BMMNC
Duan (16)	2015	China	RCT	57.88	42	12	NR	BMMNC
Gao (17)	2015	China	RCT	57.3	116	18	6.3 days	WJMSCs
Hu (N) (18)	2015	China	RCT	61.2	25	12	3–5 days	N-BMCs
Hu (HP) (18)	2015	China	RCT	59.7	25	12	3–5 days	HP-BMCs
Duan F (19)	2015	China	RCT	57.88	42	12	NR	BMC
Chullikana (20)	2014	India	RCT	47.31	20	24	2 days	BMMSC
Lee j (21)	2014	USA	RCT	53.9	48	6	NR	MSCs
Gao (22)	2013	China	RCT	55	43	12	17.1 days	BMSCs
Moccetti (23)	2012	Switzerland	RCT	55	60	60	3 days	BMC
Traverse (24)	2010	USA	RCT	52.5	40	6	4.5 days	BMC
Grajek (25)	2010	Poland	RCT	49.9	45	12	4–6 days	BMSCs
Beitnes (26)	2009	Norway	RCT	58.1	100	36	4-8 days	BMC
Herbots (27)	2009	Belgium	RCT	55	67	4	NR	BMPCs
Plewka (28)	2009	Poland	RCT	56	60	6	7 days	BMSC
Huikuri (29)	2008	Finland	RCT	60	80	6	2–6 days	BMC
Yao (30)	2008	China	RCT	54.8	47	6	13 months	BMC
Panovsky (HD) (31)	2008	Czech Republic	RCT	55	34	3	5–9 days	BMC
Panovsky (LD) (31)	2008	Czech Republic	RCT	55	30	3	5–9 days	BMC
Meluzín-2 (31)	2007	Czech Republic	RCT	48	12	6	5-9 days	BMC
Choi (32)	2007	Korea	NR	50.5	33	6	6 days	PBSCs
Zhan-quan (33)	2007	China	NR	60	58	6	NR	PBSCs
Penicka (Horak) (34)	2007	Czech Republic	RCT	59	27	4	NR	BMNCs
Ge j (Qian) (35)	2006	China	RCT	58	20	6	12 h	BMC
Meluzín-1 (LD) (36)	2006	Czech Republic	RCT	44	55	3	7 days	BMC
Meluzín-1 (HD) (36)	2006	Czech Republic	RCT	44	55	3	7 days	BMC
Hendrikx (37)	2006	Belgium	RCT	63.2	20	4	217±162 days	BMC
Janssens (38)	2006	Belgium	RCT	55.8	67	4	NR	BMSC
Kang (39)	2005	Korea	RCT	66.6	50	6	NR	PBSCs
Kang (39)	2005	Korea	RCT	59.8	36	6	NR	PBSCs
Bartunek (40)	2005	Belgium	RCT	51	38	4	11.6 days	CD133+ cells
W Ruan (41)	2005	China	RCT	61	20	6	NR	BMC
Chen (42)	2004	China	RCT	58	69	3	18.4 days	BMSCs
Wollert (43)	2004	Germany	RCT	53.4	60	6	4.8 days	BMC

Data extraction

The following data were obtained: patient information, type of stem cells, follow-up durations, outcomes, study quality. Altering in LVEF, LVESV from baseline, and LVEDV were the primary outcomes. Two authors independently conducted the steps of the systematic review. Any disagreements were discussed and resolved between reviewers.

Quality assessment

Main assessment checklist for RCTs providing by the Joanna Briggs Institute (JBI) were utilized to determine the included studies quality (13).

Data analysis

Statistical analyses were done by comprehensive CMAS. Fixed or random-effect model were used to investigate the WMD with 95% CI. Assessing the heterogeneity between the studies were done by the Cochran's Q and the I2 statistic. The I2 values more than 50 % were calculated to show a significant level of heterogeneity (14). Egger's and Begg's tests (BET) were used to obtain publication bias. p value < 0.05 for publication bias and funnel plots was considered significant.

Results

The studies included and excluded through the review process are summarized in Figure 1. In the initial search, totally 2031 records were found and then repetitious articles were deleted. Then, after screening the titles and abstracts of 1693 references, 50 papers were selected for a full-text assessment in which 30 studies (34 datasheets) met the inclusion criteria for the meta-analysis. As shown in Table 1, the studies which were conducted from 2004 to 2018, mostly in China (12 studies), with the patients mean age 55 years (from 44 to 66 old), the mean follow-up duration 9.6 months,

Tab. S2. Quality of studies used in research.

First author	Did participants analysis take place in the groups to which they were randomized ?	Did the authors conduct outcomes measurement for the treatment groups similarly?	Were all the treatment groups identical at the onset of the study?	Was contributors blindness to the treatment detected?	Was blindness to treatment assignment observed for those delivering the treatment?	Was blindness to treatment assignment observed for outcomes assessors?	Did the authors treat treatment groups identically apart from the intervention of interest?	Did the authors complete the follow up and, if not, did they describe and analyze the follow up sufficiently?	Is the concealment of group allocation to treatment groups observed?	Were the participants assigned randomly to treatment groups?	Are the analyses of outcomes measured reliably?	Do we have the correct statistical analysis?	Was a right trial plan used, and were deviations from the standard RCT plan accounted for in the conduct and analysis of the experimental?
Chullikana	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Duan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Laguna	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kang	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Qian	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Beitnes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Houtgraaf	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Meluzı´n	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Meluzı´n 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Traverse	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Choi	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hare	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bartunek	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lee	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yao	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wollert	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhan-quan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gao 2013	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gao 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Herbots	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hendrikx	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Horak	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Piepoli	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Plewka	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Panovsky	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hu-2015	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grajek	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Janssens	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Moccetti	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schachinger	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wen	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Qi	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Huikuri	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

patient total numbers 1617, and studies sample size range from 12 to 116 were selected. Notably, included studies had a low risk of bias according to the JBI tool which is shown in Table S2. Criteria were included: (1) the intervention contained of any stem cells without limitation via administration route or dose, (2) at least three months' follow-up period, and (3) in the control arm patients did not receive stem cells.

Effect of stem cell therapy on changes in LVEF, LVEDV, and LVESV after MI

A total of 29 RCTs (33 datasheets) with 1458 participants assessed the relationship between the stem cell therapy and changes in LVEF in patients after MI. In the overall pooled estimate, stem cell therapy has the capacity to change LVEF from baseline to follow-up (WMD: 2.98 mL, 95% CI: 1.66 to 4.29 mL, p = 0.00, I2 = 91 %;) (Fig. 2). Stem cell therapy and LVEDV changes interconnection was also investigated by 25 RCTs (29 datasheets) with 1324 participants. The pooled WMD was found to be –4.16 mL, 95% CI: –7.91 to –0.40 mL, P = 0.03, I2 = 78 % (Fig. 3) and thus the participants in the treatment group experienced a significant lowering in LVEDV. As well as in an overall pooled estimate, which included a total of 24 trials (27 datasheets) with 1243 participants, the patients had a significantly decrease in the cell therapy group compared to the control group in LVESV from the reference point to follow-up (WMD: –5.62 mL, 95% CI: –9.20 to –2.00 mL, p = 0.00, I = 85 %) (Fig. 4).

Publication bias

A statistical analysis of funnel plots (Figs S1–S3) suggested no publication bias BET, p > 0.05 for LVEF, LVEDV, and LVESV).

Discussion

Current study assessed the safety and ability of stem cell therapy in MI through a systematic review on the RCT studies. Although there were some contradictions on the stem cells transplantation usefulness, the result of this study is consistent with those studies indicating that stem cell therapy is an effective treatment in people, who experienced MI (45, 46).

As mentioned before, the focus of this study was on those RCT studies with the

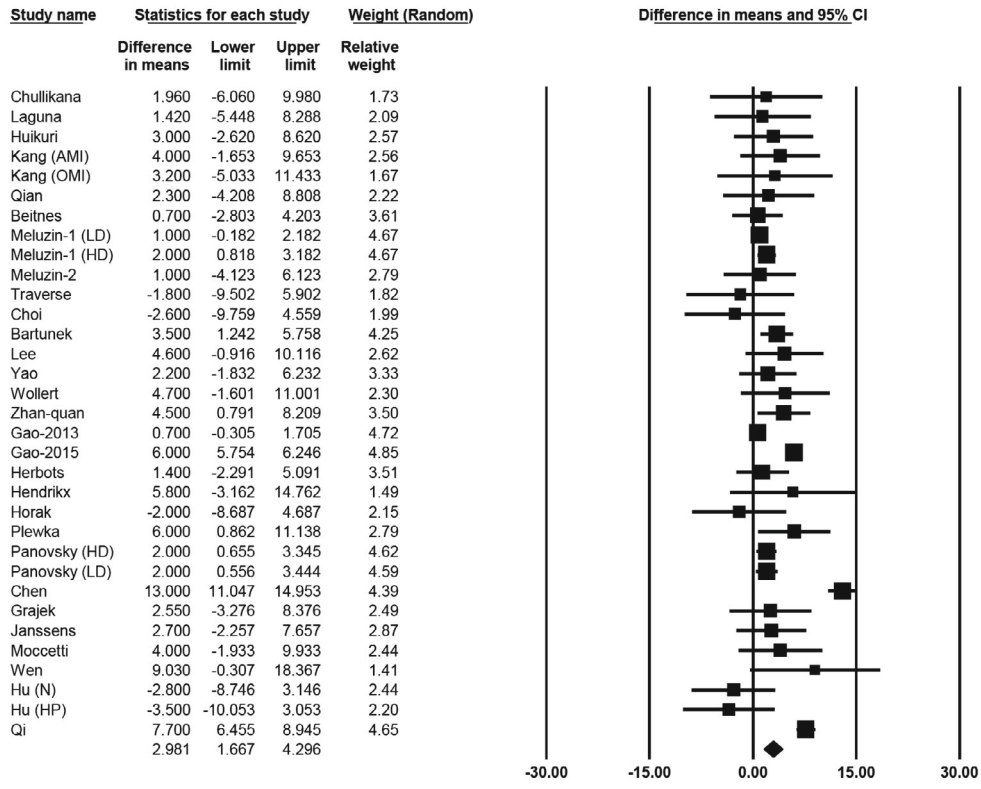

Fig. 2. Positive efficacy of stem cell therapy on changes in LVEF in post-MI cases compared to control.

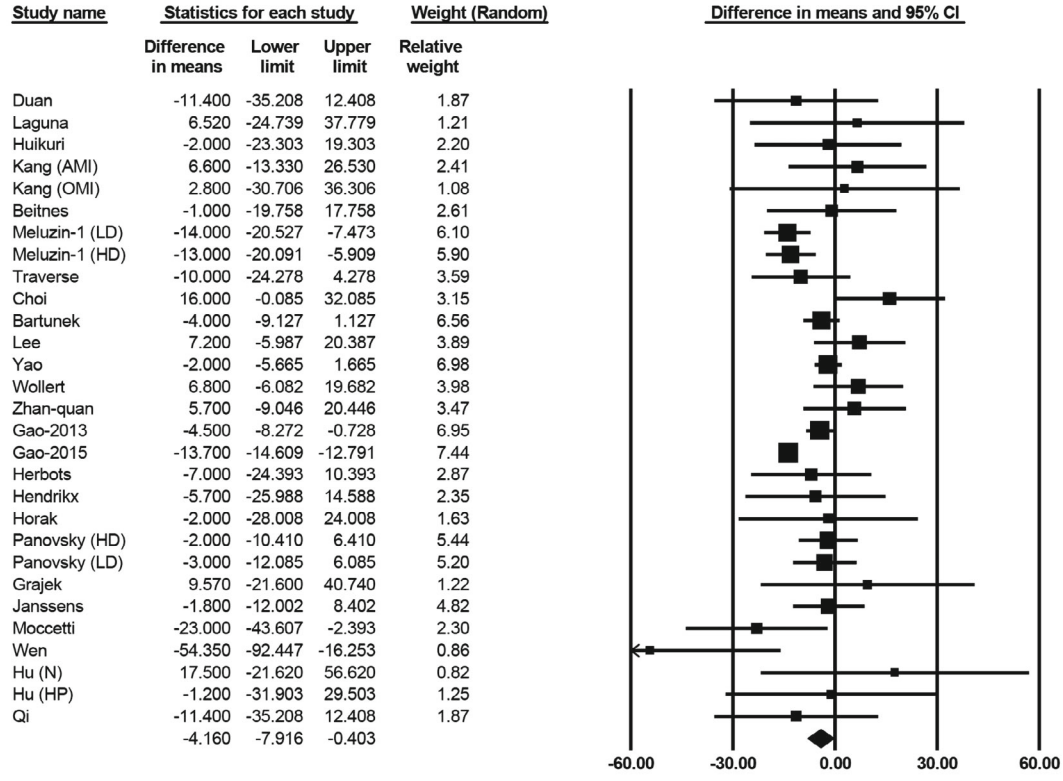

Fig. 3. Positive efficacy of stem cell therapy on changes in LVEDV in post-MI patients compared to control.

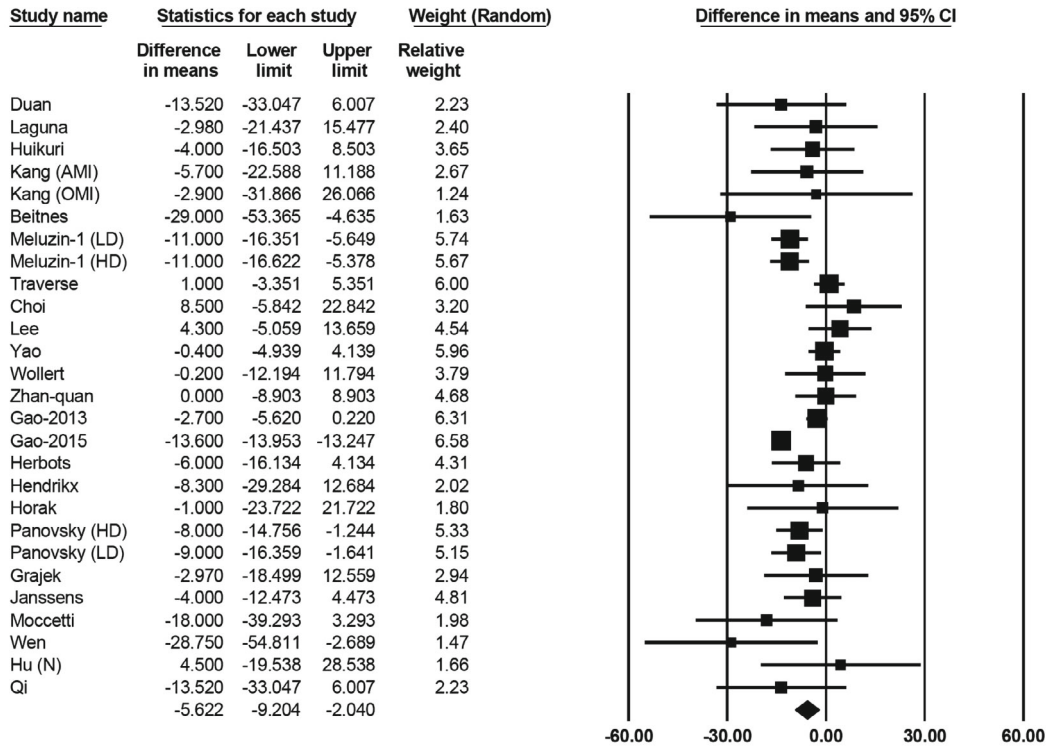

Fig. 4. Positive efficacy of stem cell therapy on changes in LVESV in post-MI patients compared to control.

following criteria; using stem cells without a restriction on administration route or dose, at least three months follow up along with the control group without receiving stem cells. Our results demonstrated that stem cell therapy had a significant impact on the LVEF and improved it from the baseline to follow-up. As well, the WMD value for LVEDV, and LVESV significantly reduced after the stem cell therapy in the treatment group compared to the control group. Ischemia and MI as a pathophysiological stimulus leads to multiple molecular and cellular processes called ventricular remodeling that results in heart failure (44, 45). The most promising goal of using stem cells as a novel treatment is its potential to convert remodeling process to regeneration process. That is why, through cardiac remodeling, cardiomyocytes loss happened as the result of different cell death pathway like apoptosis, necrosis, and autophagy. Moreover, cardiomyocytes' shape and size are affected by mechanical and neuro-humoral triggers and build-up additional extracellular matrix (ECM) leads to fibrosis (42, 43, 46, 47). It has been indicated that the stem cell therapy has the capability to change remodeling process to regeneration process by stimulation of endogenous cardiac stem cells, stimulation of angiogenesis, reduction of myocardial fibrosis, restoration of contractile function, deleterious pathological remodeling, and can induce revascularization of the injured region (45, 47). Moreover, literature also indicates that the cellular mechanisms involving exosomes, connexin, mitochondrial transfer etc. Appear to have a significant role in the cardiac renovation (45, 47). As previously explained, three predictive values, including LVEF, LVEDV, and LVESV provide an outline to estimate the efficacy of the cell therapy. Based on our investigation, at least up to 3 months' follow-up is needed to observe the positive outcome of stem cell therapy on these markers. In this way, those patients with AMI with given stem cells, showed a significant reduction in the value of LVEDV, and LVESV. This result confirmed that cell therapy was effective in preserving LV contractility similar to the previous observations (48). This study was distinctive compared to the previous study in some way. First, previous investigation was done on observational (cohorts) and interventional (non-controlled and controlled clinical trials) studies, whereas our study was concerned with RCTs only. Second, their studies investigated treated patients with AMI and IHD, whereas our work was focused on MI. Third, their analysis was based on just 11 studies with a total

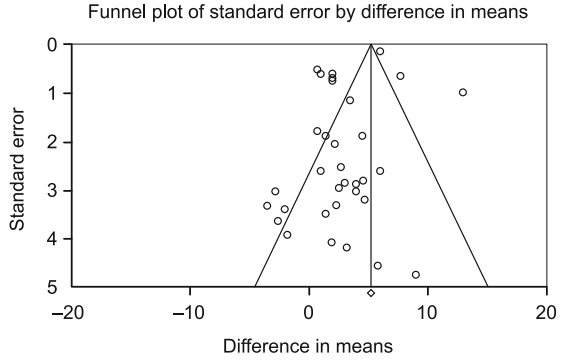

Fig. S1. Funnel plot of studies on LVEF.

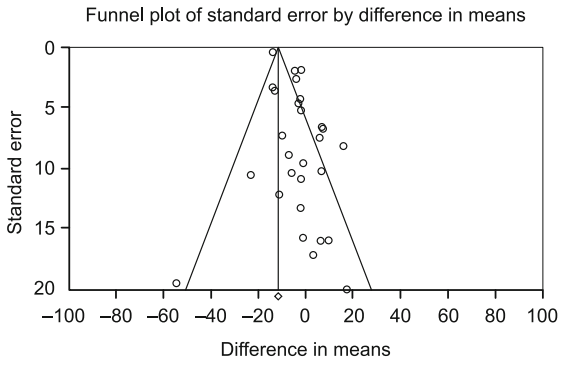

Fig. S2. Funnel plot of studies on LVEDV.

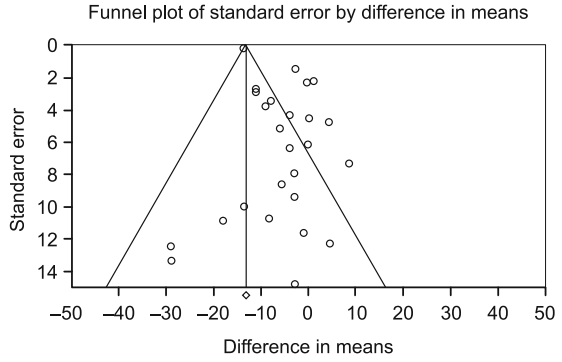

Fig. S3. Funnel plot of studies on LVESV.

of 509 participants. Even though, the current study described the efficacy of cell therapy, further investigation on a larger sample size to give more reliable results are required. Notably, this study has some limitations. First, an appreciable grade of heterogeneity was detected among the involved RCTs which might be the result of randomization nature, the timing between MI and cell therapy, the type and dose of cell infused, the infused cell quality, the methodology involved in the outcome measurements, and the baseline LVEF. Second, the analysis combined short-term with long-term outcomes as well as combined the patients with acute and chronic MI. Third, the potential influence of dose and cell injection timing could not be analyzed because of the limited information obtained from the RCTs; this might reduce the power of the conclusions (46).

Finally, important biomarkers have been identified using proteomics in connection with heart disease and effective drugs have been proposed for treatment that, along with cell therapy, can help patients recover and survive (49).

Conclusion

The present analysis provides a broad evaluation of the efficacy of cell therapy after MI. Though the outcomes of recent clinical trials showed a great deal of variety through restricted long-term follow-up, this analysis show that stem cell therapy maybe clinically pertinent and suggest a novel solution for the treatment of MI.

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