Amniotic Membrane-Derived Mesenchymal Stem Cells for Heart Failure: A Systematic Review and Meta-Analysis of the Published Preclinical Studies

Fazel Gorjipour[1], Ladan Hosseini Gohari[1], Seyed Javad Hajimiresmaiel[2], Leila Janani[3], Yousef Moradi[4,5], Hamidreza Pazoki-toroudi*[6] (ID)

Abstract

Background: Ischemic cardiomyopathies are the leading causes of mortality and morbidity. Stem cell therapy using amniotic membrane mesenchymal stem cells have emerged as a promising cardiac regeneration modality. They have shown great immunological advantage when used in allogeneic or xenogeneic transplantation. The aim of the current study is to accumulate evidence from published preclinical studies on the application of amniotic membrane derived mesenchymal stem cells (AMSCs) in the treatment of ischemic cardiomyopathies including myocardial ischemia and heart failure. The aim is to define if there is enough high-quality current evidence to support starting the use of these cells in clinical trials.

Methods: PubMed, SCOPUS, EMBASE, and ISI Web of Science databases were searched without temporal and language restrictions. Data were extracted from selected studies. The primary outcomes were left ventricular ejection fraction (LVEF) and LV fibrosis. The risk of bias (ROB) assessment was performed using SYRCLE's ROB tool. After qualitative synthesis, provided that data meets the criteria for quantitative analysis, a meta-analysis was performed using Stata software V12 to investigate the heterogeneity of the data and to get an overall estimate of the effect size of the treatment on each outcome.

Results: On primary search, 438 citations were retrieved. After screening, three studies were selected for quantitative analysis of each of the outcomes LVEF and LV fibrosis. Their administration in acute and chronic MI alleviates heart failure and improves LVEF (SMD=3.56, 95% CI: 2.24-4.87, I-squared=83.1%, p=0.003) and reduces infarct size (SMD= -4.41, 95% CI: (-5.68)-(-3.14), I-squared=79.0%, p=0.009). These observations were achieved in the acute MI model, HF following ischemia due to coronary artery stenosis and coronary artery occlusion with the early restoration of the perfusion.

Conclusion: Present low and medium quality evidence from preclinical studies confirm the efficacy of the AMSCs in the preclinical models of acute MI and HF following ischemia due to coronary artery stenosis and permanent/temporary coronary artery occlusion. High-quality preclinical studies are indicated to bridge the gaps in translation of the current findings of AMSCs research for the treatment of patients with acute and chronic myocardial ischemia and heart failure.

Keywords: Preclinical Studies, Ischemic Cardiomyopathy, Myocardial Ischemia, Heart Failure, Ischemic Heart Diseases, Mesenchymal Stem Cells, Stem Cell Therapy, Amniotic Membrane, Amnion

Introduction

Reperfusion injury, tissue remodeling and inappropriate

regeneration after myocardial ischemia results in the de-

Corresponding author: Dr Hamidreza Pazoki-toroudi, pazoki.h@iums.ac.ir

1. Cellular and Molecular Research Centre, Iran University of Medical Sciences, Tehran, Iran
2. Department of Cardiology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran
3. Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
4. Social Determinants of Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
5. Department of Epidemiology and Biostatistics, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
6. Physiology Research Center and Core Facilities, Iran University of Medical Sciences, Tehran, Iran

↑What is "already known" in this topic:
Mesenchymal stem cells from amniotic membrane have shown promise for cellular therapy in heart failure. Reports demonstrated their positive effects on the cardiac function and myocardial fibrosis.

→What this article adds:
Quality of the existing evidence is investigated. Whether the available evidence supports entering the clinical trials is discussed. Translational gaps in the clinical application of these cells are described.

velopment of fibrosis, impairment of myocardial function and heart failure (1, 2). Patients suffering from end-stage heart failure are indicated for heart transplantation. Due to lack of organ donation, donor matching and long-term problems associated with it, many people require alternative therapeutic approaches (3). Moreover, current mechanical circulatory assist devices are expensive and not yet fully developed, requires complicated surgical intervention for implantation and persistent monitoring due to potential for device failure (4). Stem cell therapies especially using mesenchymal stem cells (MSCs) have demonstrated promising results (5, 6). However, due to concerns with scalability and other problems associated with autologous stem cell therapy, proper allogeneic cells with desirable immunological compatibility are required (7, 8). Studies have suggested fetal adnexa including amniotic membrane as a rich source of MSCs (AMSCs) which are highly immunologically tolerated after allo- and xenotransplantation in animal models of myocardial ischemia (9, 10). These cells could be easily obtained from the amniotic membrane, which is usually discarded after childbirth (11, 12). Their immunological compatibility, proangiogenic capacity, growth properties and expansion potential make them an appropriate source for scalable off-the-shelf stem cell therapies (12). AMSCs have shown efficacy in treating MI and heart failure in animal models in some studies (9, 10, 13); however, summarizing the studies to identify the gaps in translation of the findings to viable therapies for cardiomyopathies is required. The study was conducted to systematically review the preclinical studies on the application of mesenchymal stem cells from the amniotic membrane (AMSCs) in the treatment of myocardial ischemia and heart failure and to identify the potential gaps in its safety and efficacy studies for entering human trials.

This systematic review is aimed to address the following questions:

1- What are the effects of AMSCs on the cardiac function (including Left ventricular ejection fraction (LVEF) and fractional shortening (FS)) after myocardial ischemia in comparison with untreated ischemia group in animal models?

2- What are the effects of AMSCs on myocardial tissue fibrosis following myocardial ischemia and heart failure in animal models?

3. What are the dosing schedules, administration routes and modes of transplantation (autologous, allogeneic or xenogeneic), have been used in the treatment of myocardial ischemia and heart failure with AMSCs in animal models and what are their outcomes?

Methods
The Preferred Reporting Items for Systematic Review and Meta-Analysis was used for preparing and reporting this systematic review. In addition, the PRISMA Flow Diagram is employed to describe the flow of information through the different phases of this systematic review.

Inclusion criteria
We included all original research in animal models on the application of AMSCs from the human amniotic membrane or their derivatives for the treatment of disease models of acute or chronic myocardial infarction (MI), heart failure, ischemic cardiomyopathies and coronary artery diseases.

Exclusion criteria
Regrading the studies published in duplicate or presented the same data in more than one article, the one describing more data and the updated one were used and the other(s) were excluded from the study. Studies not including primary data or lacks quality standards according to the critical appraisal checklist, were excluded as well.

Search methods for the identification of relevant studies
Electronic searches: PubMed, SCOPUS, EMBASE, and ISI Web of Science databases were searched with appropriate search strategies without language and temporal limits.

Database search was performed with two different researchers (GHL and FG), and the retrieved citations were pooled for subsequent selection independently.

PubMed search strategy: #1. "Ischemia"[Mesh] OR "Infarction"[Mesh] OR "reperfusion injury"[MeSH Terms] OR ischemia [Text Word] OR infarction [Text Word] OR failure [Text Word] OR reperfusion [Text Word] OR ("reperfusion"[Text Word] AND "injury"[Text Word]) OR "reperfusion injury"[Text Word]

#2. "coronary arter*"[Text Word] OR "left ventricle"[Title/Abstract] OR myocard*[Title/Abstract] OR cardiac[Title/Abstract] OR heart[Title/Abstract] OR cardiomyocyt*[Title/Abstract] OR ventricular[Title/Abstract] OR "Myocardium"[Mesh] OR "Myocytes, Cardiac"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Coronary Vessels"[Mesh] OR "Heart"[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR "Heart Ventricles"[Mesh] OR "Ventricular Remodeling"[Mesh]

#3. #1 AND #2

#4. "Heart Failure"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Inferior Wall Myocardial Infarction"[Mesh] OR "Anterior Wall Myocardial Infarction"[Mesh]

#5. #3 OR #4

#6. amnion [Text Word] OR "amniotic membrane"[Text Word] OR "amnion"[Mesh]

#7. "Mesenchymal Stromal Cells"[Mesh] OR "Mesenchymal Stem Cell Transplantation"[Mesh] OR mesenchymal[Title/Abstract] OR stromal[Title/Abstract] OR "mesenchymal stem cell*"[Text Word] OR "mesenchymal stromal cell*"[Text Word]

#8. hAMCs[Title/Abstract] OR hAMSC[Title/Abstract]

#9. #6 AND #7

#10. #8 OR #9

#11. #5 AND #10

#12. #11 [filter: Animals-SYRCLE]

Searching other sources: Reference lists of relevant primary studies, reviews, and key journals were searched

for additional studies. Key journals include but not limited to the journals by American Heart Association (AHA) including "Circulation", "Circulation Research" and "Heart Failure".

Data collection and analysis

Selection of studies: Retrieved articles first were checked in two phases. Pre-selection was performed based on title/abstract screening and the original studies regarding the application of stem cells for myocardial ischemia were identified based on predefined inclusion and exclusion criteria. Two researchers (MY and GF) independently evaluated and appraised the results of the searches, based on the title and abstract. In cases of discrepancies over the selection, a third referee made a decision about inclusion or exclusion of the article. Likewise, reviewers screened the full-text of pre-selected studies for final selection based on predefined criteria.

Data extraction and management

A data extraction form was prepared for registration of extracted data. When there is no agreement on the data selection process, a third researcher will help in making the final decision.

The following data were extracted from all the included studies:

1. Study characteristics (author, publication year, sample size, journal, outcomes, and methods of measurement, animal model species, model generation method, number of groups and duration of observation) were recorded.

2. Participants' characteristics (age, sex, weight, baseline and secondary measurements of cardiac function, pathologic findings and molecular findings)

Corresponding authors of selected studies for which some data are missing were contacted by email to request for information. Eligible studies were categorized according to the type of animal model generation and species of studied animals as well as the type of transplant- autologous, allogeneic, or xenograft- they are receiving.

In selecting the data according to the outcome measures, priority was given to studies reporting cardiac function and tissue fibrosis. Any disagreements regarding the inclusion of studies were resolved by discussion or by consulting a third author. A checklist of all included studies along with the tables summarizing the data was documented and the reasons for exclusion of studies were recorded in this document.

Assessment of risk of bias in included studies

a) Two reviewers will independently assess the risk of bias/study quality of each study.

b) Discrepancies were made by consensus between two reviewers, and if the discrepancy remained unresolved, a third reviewer helped make a decision.

The SYRCLE's Risk of Bias tool was used for the assessment of the internal validity of included studies (e.g., selection, performance, detection and attrition bias) and/or other study quality measures (e.g., reporting quality, power).

Data synthesis

Included studies were overviewed and presented in two separate tables: one provides details on study quality according to the mentioned tool, and the other table include the study design, cell donors, and specifications of the subjects (including animal species, method for induction of the disease and cell administration route).

Two steps of statistical inspection of the primary measures were intended

(1) identification of data sources and documenting estimates, and (2) a random-effects and fixed-effects meta-analysis model to aggregate prevalence estimates and to account for variability between studies, by calculating the overall pooled estimate and the 95% CI.

The mean differences in myocardial function (EF) between controls (sham groups) and treatment groups were pooled by way of a meta-analysis using Stata software (Stata Corp V.12, Texas, USA).

I^2 heterogeneity statistic was used for the assessment of heterogeneity between the included studies reported as a percentage (%)to estimate the extent of variation between the studies. Categories of heterogeneity with a value of ≤25% as low, 26–50% moderate, 51–75% substantial, and 76–100% as considerable heterogeneity defined by Higgins (14). Furthermore, Forest plots were used to identify heterogeneity by means of the χ2 test (with significance defined at the α-level of 10%) and the I^2 statistic (where ≥50% indicates substantial heterogeneity).

Sensitivity analysis

Sensitivity analysis was performed according to different languages, quality of studies, and differences in countries when appropriate.

Subgroup analyses

Subgroup analysis was intended when appropriate. The analysis was performed if a sufficient number of studies were available. For example, according to the mode of animal model induction, mode of transplantation (xenogeneic or allogeneic), animal species and methods of outcome assessment (for example, MRI or echocardiography for cardiac function or methods of cell death detection).

Reporting of this review

We used preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram to summarize the selection process of articles and the reason for the selection or exclusion of studies in detail. The systematic review is prepared and published based on the latest edition of the PRISMA guidelines. The quality appraisal was based on SYRCLE's RoB tool.

Results

As summarized in Figure 1 (PRISMA flow diagram of the study), 438 reports were identified using database search using predefined search strategy and hand searching, and 427 studies were excluded during the initial
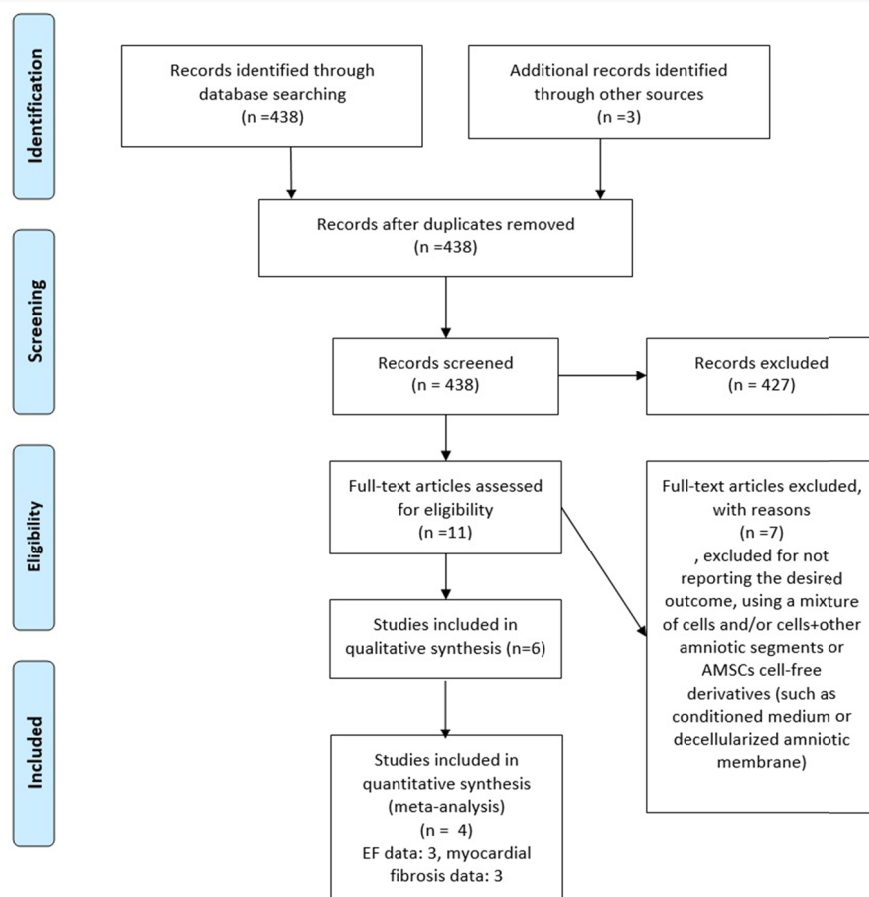
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the current study

screening because they were not original studies or did not include experimental studies. Eleven articles were retrieved in full-text and screened according to the inclusion and exclusion criteria. Two studies had used amniotic epithelial cells; one used decellularized amniotic membrane, one used MSCs from amniotic fluid and one used conditioned medium from human amnion-derived mesenchymal stem cells. After the full-text screening, six studies were selected for qualitative data synthesis (Table 1) and three of the studies were suitable for quantitative data synthesis. Data from three studies were pooled for meta-analysis.

The risk of bias assessment using SYRCLE's ROB tool demonstrated that there is a high risk of bias in the selected studies. The most probable risk of bias types including attrition bias, where no explanation of missing animal data was presented and selection bias due to no evidence of adequate concealment of groups. Another potential source of bias in these studies was random housing of animals in the cages and all of these studies do not provide any evidence on random housing of the animals (Fig. 2, Table 2).

Fujimoto et al. (2009) reported that the administration of ADMSCs following acute MI reduced postinfarction LV cavity dilatation and improved LV systolic function (15). Tsuji et al. (2010) proved that treatment with these cells two weeks after MI improves fractional shortening (10). A study by Kimura et al. (2012) demonstrated that LVEF was significantly improved and LV dilatation was

well attenuated 4 weeks after AMSC transplantation in swine models of chronic myocardial ischemia induced by Ameroid constrictor deployment on the LAD (9). Kim et al. (2013) demonstrated that the administration of AD-MSC after acute MI in mice results in reduced LVEDD and LVESD and elevated EF compared to the control group in a four-week follow-up (13). Dash et al. (2015) demonstrated that the treatment of swine pig models of myocardial I/R injury improves EF in the treated group and reduces chamber dilatation compared with the control group in a six-week follow-up (16). Only three studies were reporting EF as outcome measures (Kimura et al. 2012, Kim et al. 2013, and Dash et al. 2015) (9, 13, 16). The quantitative meta-analysis revealed that the use of AMSCs has meaningfully improved the LVEF (SMD= 3.56; 95% CI=2.24-4.87). However, a strong heterogeneity between studies was observed (I-squared=83.1%; p=0.003) (Fig. 3).

Fujimoto et al. (2009) claimed a reduction of fibrosis area but they did not provide a quantitative measure of it; also they present data regarding improved ventricular wall thickness (15). Tsuji et al. (2010) reported decreased fibrosis area in the cell therapy group compared with the control group (10). Kimura et al. (2012) demonstrated that ADMSC administration in chronic myocardial ischemia reduces myocardial fibrosis (9). Kim et al. (2012) demonstrated that these cells are more effective than adipose-derived mesenchymal stem cells in reducing the tissue

Table 1. Summary of the six studies included in the qualitative systematic review

Study number	Author-year	Journal	Donor spec.- mode-acceptor spec.	Administration	Manipulations/adjuvants	Animal model
(1)	Zhao P, et al. 2005	Transplantation	Human amniotic mesenchymal cells (hAMC)- Xenograft-female Sprague-Dawley rats	Injection into the infarcted area at two or three sites	PKH26-labeling	Occlusion of the left anterior descending branch of the left coronary artery
(2)	Fujimoto KL, et al. 2009	Cell Transplantation	AMCs from Lewis rat-allograft- female Lewis rats	Injection into the infarcted area at four sites	No manipulation	Proximal left coronary ligation
(3)	Tsuji H, et al. 2010	Circulation Research	Human amniotic mesenchymal cells (hAMC)- Xenograft-Wistar rats	Injection into the infarcted area at two or three sites	EGFP-labeled hAMCs were injected into the myocardium at the border zone of the MI	Left anterior coronary artery ligation by 6 – 0 silk suture
(4)	Kimura M, et al. 2012	Journal of Stem Cells and Regenerative Medicine	Porcine AMSCs-Allograft-Pigs	Epicardial injection into the ischemic region at 16–20 locations with a 25-gauge needle	No manipulation	Ameroid constrictor implantation around the left circumflex coronary artery
(5)	Kim S, et al. 2012	International Journal of Cardiology	Human AMSCs - Xenograft- In NOD/SCIDmice (NODCB17-Prkdcscid/J strain mice)	An intra-myocardium injection of 40 μl delivered into 5 sites in the border zone of the infarcted region (apical lateral, apical anterior, basal anterior, mid anterior and mid lateral).	No manipulation	Left anterior descending artery (LAD) occlusion with an 8.0 nylon suture
(6)	Dash R, et al.- 2015	Journal of the American Heart Association	hAMSCs- Xenograft-pigs	Intramyocardial delivery to 8 infarct and peri-infarct zones using the Helix Helical Infusion System, a distal helical needle, and a Morph Universal Deflectable Guide Catheter	Transduction with a double-fusion PET-RG containing firefly luciferase for bioluminescence and herpes simplex virus thymidine kinase (HSV-tk) for PET.	Left anterior descending coronary ischemia–reperfusion injury for 60 minutes
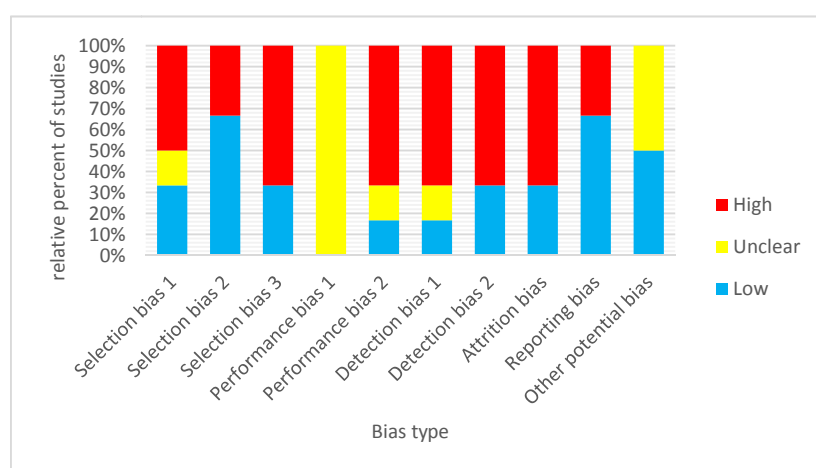
Fig. 2. Risk of bias score for each risk item in animal studies of the amniotic mesenchymal stem cells (AMSCs) for heart failure and ischemic cardiopmyopathies, as assessed using the SYRCLE ROB tool.

fibrosis when administered immediately after ischemia in acute MI model (13). Dash et al. (2015) used manganese-enhanced magnetic resonance imaging (MEMRI) and delayed gadolinium enhancement magnetic resonance imaging (DEMRI) to study the peri-infarct region (PIR) viability in infarcted myocardium in a swine model. Digital subtraction of MEMRI-negative myocardium (intra-infarct region) from DEMRI–positive myocardium (PIR and intra-infarct region) clearly delineated the PIR (16). The MEMRI-positive signal in this PIR region of the in-

Table 2. Risk of bias assessment of the studies included in qualitative data synthesis using SYRCLE's ROB tool

Study	1	2	3	4	5	6	7	8	9	10
	Selection bias 1	Selection bias 2	Selection bias 3	Performance bias 1	Performance bias 2	Detection bias 1	Detection bias 2	Attrition bias	Reporting bias	Other potential bias
Zhao P, et al. 2005	X	X	X	?	?	?	X	X	✓	?
Fujimoto KL, et al. 2009	✓	✓	X	?	X	X	X	X	✓	?
Tsuji H, et al. 2010	✓	✓	✓	?	✓	✓	✓	X	✓	✓
Kimura M, et al. 2012	X	✓	X	?	X	X	X	✓	X	✓
Kim S, et al. 2012	?	X	✓	?	X	X	✓	X	✓	✓
Dash R, et al. 2015	X	✓	X	?	X	X	X	✓	X	?

1 ✓ = Adequate randomization; ? = randomized but no details; x = no evidence of randomization.
2 ✓ = Baseline characteristics given; x = baseline characteristics not given.
3 ✓ = Evidence of adequate concealment of groups; x = no evidence of adequate concealment of groups.
4 ✓ = Evidence of random housing of animals; ? = unknown housing arrangement.
5 ✓ = Evidence of caregivers blinded to intervention; x = no evidence of caregivers blinded to intervention.
6 ✓ = Evidence of random selection for assessment; x = no evidence of random selection for assessment.
7 ✓ = Evidence of assessor blinded; x = no evidence of assessor blinded.
8 ✓ = Explanation of missing animal data; x = no explanation of missing animal data.
9 ✓ = Free of selective reporting based on methods/results;? = insuive reporting; x = selective reporting.
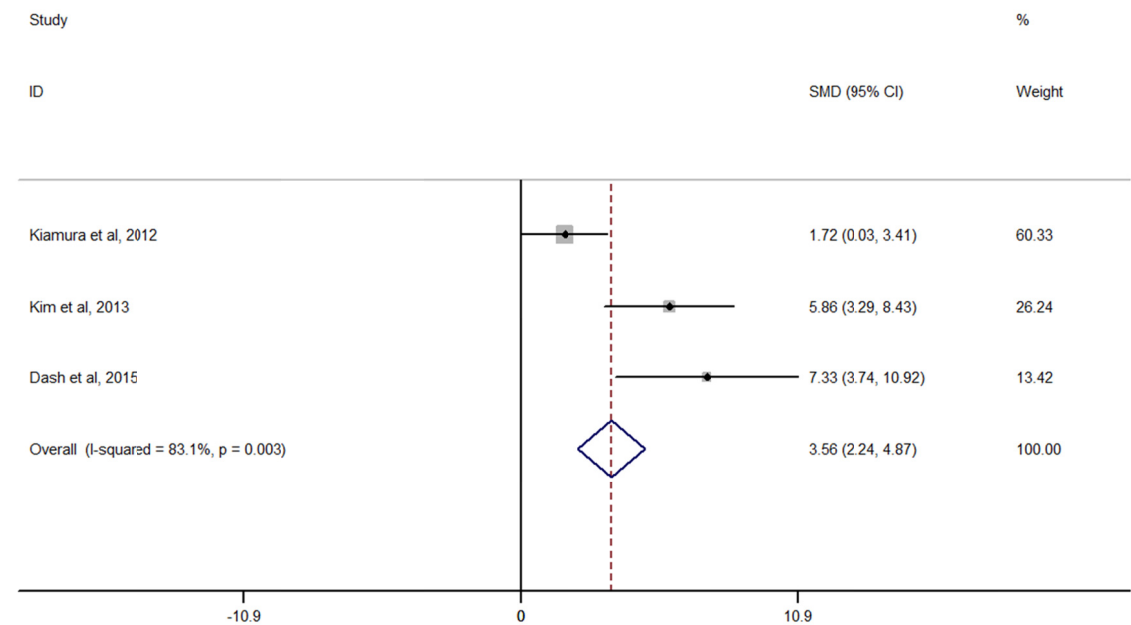10 ✓ = Free of other high bias risk; ? = insufficient data to determine risk of other bias.

Fig. 3. Forest plot demonstrating the pooling of the data from studies reporting the changes in ejection fraction (EF) in animal models of ischemic cardiomyopathies treated with amniotic mesenchymal stem cells (AMSCs). SMD represents the standardized mean difference in percent EF of the left ventricle in diseased animals treated with AMSCs in comparison with diseased control animals without treatment.

jured heart reflected its viability and the restorative potential. Using this approach, they demonstrated that percutaneous administration of the ADMSCs in the I/R injury of pig myocardium improved PIR viability and restorative potential. Data from three of these studies were included in the meta-analysis (9, 10, 13). The quantitative meta-analysis revealed that the use of AMSCs has meaningfully decreased the myocardial fibrosis of the left ventricle (SMD= -4.41; 95% CI;-5.68, -3.14). Again, a strong heterogeneity between studies was observed (I-squared=83.1%; p=0.003) (Fig. 4).
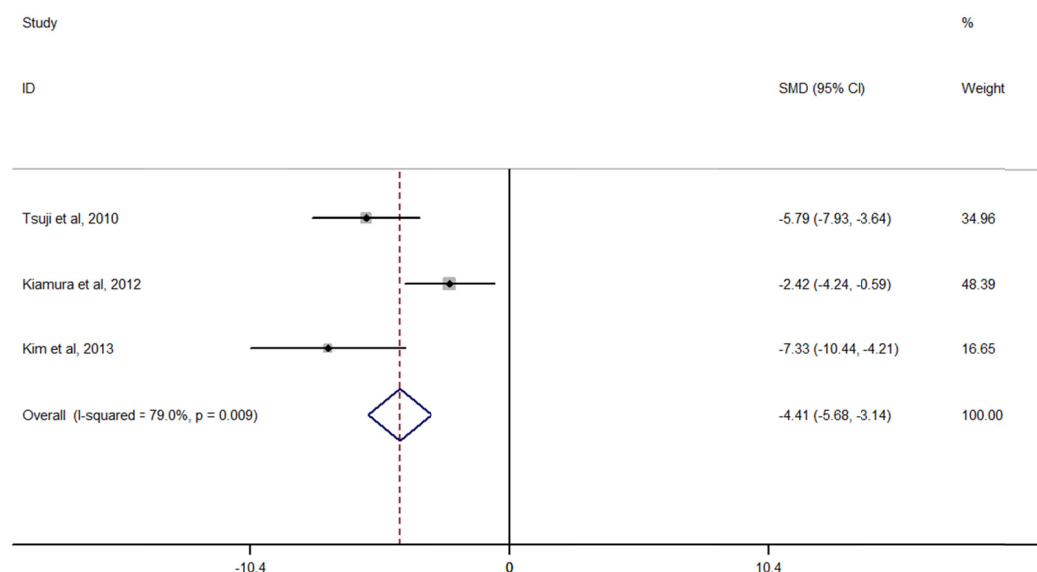
Fig. 4. Forest plot demonstrating the pooling of the data from studies reporting the changes in tissue fibrosis in animal models of ischemic cardiomyo-pathies treated with amniotic mesenchymal stem cells (AMSCs). SMD represents the standardized mean difference in percent area of the fibrosis of the left ventricle in diseased animals treated with AMSCs in comparison with diseased control animals without treatment.

Discussion

Many animal studies have reported favorable properties of mesenchymal stem cells from various sources in the treatment of ischemic cardiomyopathies by reducing the myocardial infarct size and improving left ventricular ejection fraction (9, 10, 13, 15-18). However, discrepancies exist in the results of clinical trials aiming to reduce myocardial injury by the administration of MSCs (19, 20). Some of these studies reported no beneficial effect of MSC on myocardial ejection fraction and improvement of other clinical outcomes in patients with heart failure (5). There appears to be a gap in the translation of findings from preclinical studies to viable cell therapies for patients. In the current study, we tried to address this gap by systematically reviewing the current evidence on testing the AMSCs for the treatment of myocardial ischemia and heart failure in preclinical studies and identifying unmet needs. The AMSCs has not been applied in clinical trials yet but evidence supports that it is a very valuable candidate for use in these patients (9, 13, 16, 21). Our current study is the first to systematically evaluate the effect of AMSCs on ischemic cardiomyopathies and subsequent heart failure in animal models in terms of cardiac function and myocardial fibrosis.

Our study demonstrated that these cells effectively improve left ventricular ejection fraction and reduce left ventricular fibrosis when administered after acute ischemia and ischemia/reperfusion injury, hinting the value of timely intervention following ischemic insult for sparing the myocardium from acute injury and to alleviate it (13, 15, 16, 22). It is also proved effective in the treatment of a pig model of chronic ischemic heart failure when the model was generated by using an Ameroid constrictor stenosis of the proximal LAD (17). However, the use of AMSCs in myocardial regeneration some more advanced states of the disease following complete closure of LAD with severe fibrosis and remodeling of the ventricular muscles need investigation. Despite positive outcomes following the use of these cells in the models of ischemic cardiomyopathies in meta-analysis, there is a high heterogeneity between studies. This heterogeneity my rise from reasons such as variations in the size of animals (small or large), the animal model species specific characteristics, mode of transplantation (allogeneic or xenogeneic), time interval of the ischemia and cell transplantation and the nature of animal model. Types of the animal models used include acute ischemia with permanent ligation of LAD (22), chronic ischemia with coronary stenosis (induced by Ameroid constrictor deployment) (9) and acute ischemia with early revascularization (ischemia/reperfusion injury by balloon inflation and deflation) (21). These varieties in animal models and time of intervention may resemble the wide variety of pathology of the disease observed in clinical conditions which is a strength point of the available evidence, on the other hand it makes it difficult to make a conclusive decision regarding the use of these cells and a valid protocol for human use. For use of these cells in human trials it is suggested that first a safe dose for human studies be identified, then to define a standard time and route of administration.

Another shortage is the lack of strong evidence regarding the use of these cells in models of congestive heart failure, which is a priority condition for the use of stem cell therapies. This stage of the disease is characterized by advanced heart failure and patients usually does not respond to the existing therapies. Animal models are generated by ligation of the LAD or cryoinjury and animals usually develop congestive heart failure by four weeks

next to the operation (18, 23-27).

Another cause for concern is the quality of the published studies. Assessment of the reporting quality demonstrates that there is a shortage of high quality studies about different aspects of the use of these cells for the treatment of myocardial ischemia and heart failure. This warrants further high quality in vivo studies before entering human trials.

Conclusion

In sum, it appears that in vivo research on the use of AMSCs in the treatment of heart failure and ischemic cardiomyopathies are premature and further high quality investigations are required. Current evidence demonstrates that early administration of AMSCs is effective in the treatment of ischemic cardiomyopathies in mild to moderate conditions, however its benefits in the treatment of severe ischemic cardiomyopathies and advanced heart failure needs further investigation. Available results are promising.

Conflict of Interests

The authors declare that they have no competing interests.

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