International Journal of Cardiology 177 (2014) 764–770

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Effectiveness and safety of selected bone marrow stem cells on left ventricular function in patients with acute myocardial infarction: A meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 29 April 2014
Received in revised form 9 September 2014
Accepted 1 November 2014
Available online 4 November 2014

Keywords:
Selected bone marrow stem cells
Acute myocardial infarction
Randomized controlled trials
Meta-analysis

ABSTRACT

Background: Concerns regarding the use of selected bone marrow stem cells (BMSCs) in the field of cardiac repair after acute ischemic events have been raised. The current meta-analysis aimed to assess the efficacy and safety of selected BMSC transplantation in patients with acute myocardial infarction (AMI) based on published randomized controlled trials (RCTs).

Methods: A systematic literature search of PubMed, Ovid LWW, BIOSIS Previews, and the Cochrane library from 1990 to 2014 was conducted. Results from RCTs involving subjects with AMI receiving selected BMSC therapy and followed up for at least 6 months were pooled.

Results: Eight trials with a total of 262 participants were included. Data were analyzed using a random effects model. Overall, selected BMSC therapy improved left ventricular ejection fraction (LVEF) by 3.17% (95% confidence interval [CI] 0.57–5.76, P = 0.02), compared with the controls. There were trends toward reduced left ventricular end-systolic volume (LVESV) and fewer major adverse cardiac events (MACEs). Subgroup analysis revealed a significant difference in LVEF in favor of selected BMSC therapy with bone marrow mesenchymal stem cells (BMMSCs) as the cell type.

Conclusions: Transplantation of selected BMSCs for patients with AMI is safe and induces a significant increase in LVEF with a limited impact on left ventricular remodeling.

1. Introduction

Acute myocardial infarction (AMI) remains a major cause of death and disability despite remarkable progress in therapeutic approaches, including the development of new medications, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Myocardial ischemia leading to a loss of contractile tissue has been established as the critical cause for disruption of the mechanical performance of the left ventricle in patients with AMI [1]. In this respect, stem cell therapy-mediated differentiation into cardiomyocytes and subsequent angiogenesis has emerged as a novel alternative option to repair damaged myocardium. Although numerous experimental and clinical trials [2–4] and meta-analyses [5,6] have demonstrated the benefits of unselected bone marrow stem cells (BMSCs) on myocardial ischemia, the mechanisms by which multiple cells derived from the bone marrow function in cardiac repair remain unclear. Meanwhile, disillusionary outcomes have also been reported.

Significant progress has been made in the identification and clinical grade purification of several types of progenitor cells. Preclinical studies indicate that selected progenitor cells contribute to the revascularization of ischemic regions in the infarcted myocardium, and this event is proposed to be associated with their paracrine effects, differentiation into cardiomyocytes, and angiogenesis. RCTs with selected BMSCs, including many well-defined progenitor cell types [1,7–13], such as CD133+, CD34+ and bone marrow mesenchymal stem cells (BMMSCs), have been performed in patients with AMI. Notably, these earlier trials were conducted in a relatively small number of patients, which may attenuate the efficacy of selected BMSCs. Accordingly, the current meta-analysis was performed to accurately establish the efficacy and safety of selected BMSCs for patients with AMI on the basis of collective data from published RCTs.

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http://dx.doi.org/10.1016/j.ijcard.2014.11.005
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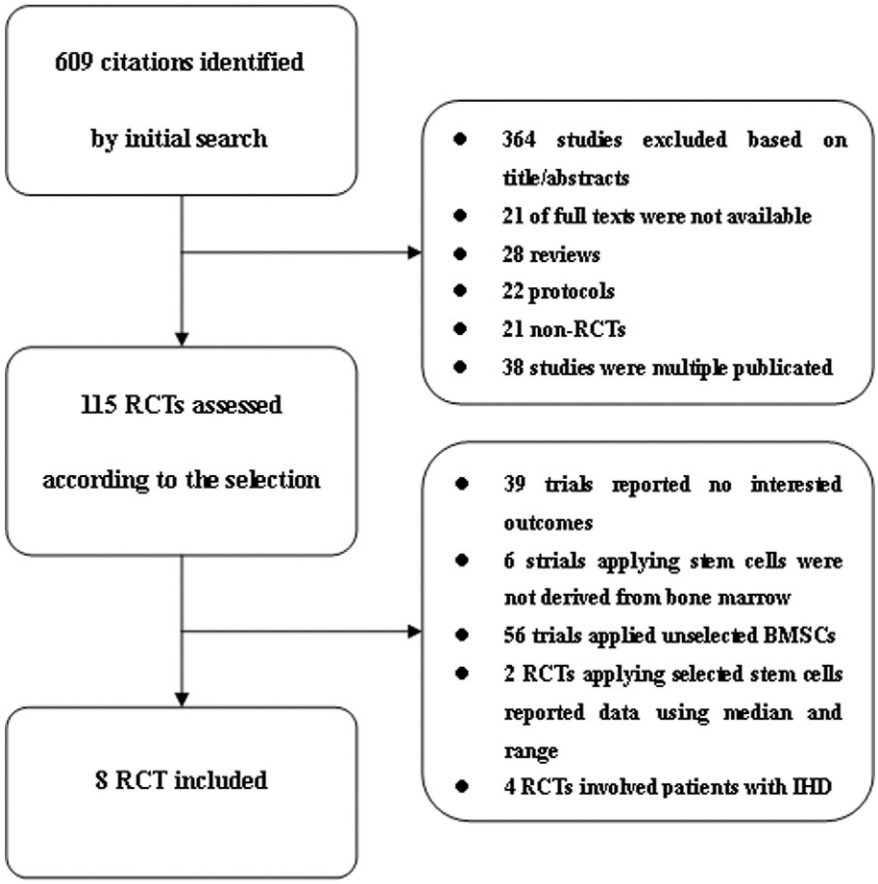

Fig. 1. Flow diagram of studies included in the meta-analysis. RCTs, randomized controlled trials; BMSCs, bone marrow stem cells.

2. Methods

2.1. Eligibility criteria

RCTs were included based on the following criteria: (1) published, prospective trials, (2) patients were clinically diagnosed with AMI, (3) the transplanted cell type was limited to purified autologous or allogeneic BMSCs with no restrictions in terms of dose or administration route, and (4) participants in the comparator arm received standard therapy rather than stem/progenitor cells. The exclusion criteria for studies were as follows: (1) patients were diagnosed with chronic ischemic heart disease, (2) transplanted cells were unselected BMSCs, (3) circulating/peripheral progenitor cells were mobilized from bone marrow with granulocyte colony stimulating factor (G-CSF), (4) subjects with angina rather than myocardial infarction were included, (5) no LVEF data were available, (6) less than 6 months of follow-up were recorded, (7) data were presented as median and range, or (8) publications were in languages other than English.

2.2. Search strategy

RCTs were identified from searches of PubMed (1990–2014), Ovid LWW (1997–2014), BIOSIS Previews (1990–2014), and the Cochrane library (Cochrane Database for Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and ACP Journal Club, 1999–2014) using the following terms: "stem cells," "progenitor cells," "bone marrow cells," "coronary artery disease," "myocardial infarction," "acute myocardial infarction," "ischemic cardiomyopathy," "cardiomyopathy," and "heart failure." In addition, we manually searched the reference lists of all original articles and previous systematic reviews.

2.3. Data extraction

Two investigators independently screened all titles and abstracts to identify studies that met the inclusion criteria. Relevant data regarding baseline characteristics, stem/progenitor cell type, duration of follow-up, LVEF and LV volumes, and major adverse cardiac events (MACEs) were extracted (as available) from individual studies. Clinical trials with multiple publications, sequential follow-up durations or different outcome indicators were considered as a single study. Magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) data were preferred over echocardiographic data for primary analysis, where available.

2.4. Study outcomes

The primary end point was taken as changes in LVEF from baseline to follow-up. Changes in the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and the incidence of MACEs were considered the secondary endpoints.

2.5. Statistical analysis

Cochrane Review Manager 5.2 was applied for quantitative analysis of outcome data. Both fixed and random effects models were used, and the latter were preferred in cases of heterogeneity beyond that expected by chance. Continuous outcomes were expressed as weighted mean differences with 95% confidence intervals (CI). I^2 statistic and the χ^2 test were used to examine heterogeneity. Values of $I^2 > 50\%$ were indicative of a substantial level of heterogeneity. Potential reasons for observed heterogeneity were explored with

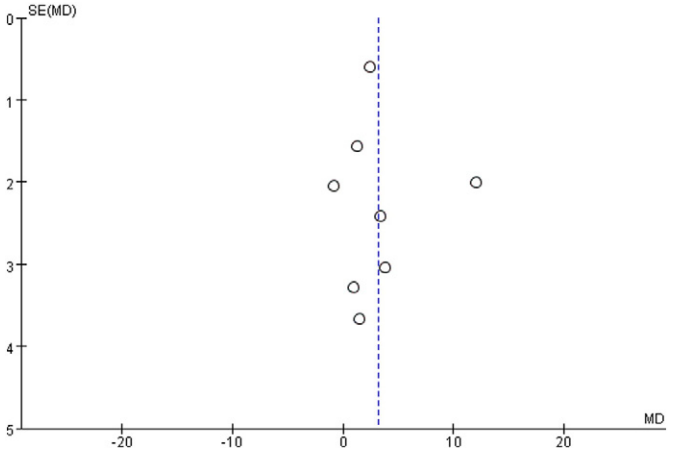

Fig. 2. Funnel plot for left ventricular ejection fraction outcome data of the included studies.