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Meta Analysis

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

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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 (*CI*s). We collected individual trial data and conducted a meta-analysis to compare changes in global left ventricular ejection fraction (ΔLVEF) 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 ΔLVEF between the bone marrow stem cells (BMCs) group and control group when the dose of BMCs was $\leq 1 \times 10^7$ [ΔLVEF *95% CI*: 0.12−3.96%, $P = 0.04$]. The ΔLVEF in the BMCs groups was significantly higher than in the control groups when the dose of BMCs was $\leq 1 \times 10^8$ [ΔLVEF *95% CI*: 0.95−4.25%, $P = 0.002$] and $\leq 1 \times 10^9$ [ΔLVEF *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 [ΔLVEF *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.

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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.

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 $\geq$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