Chin Med Sci J
September 2016

Vol. 31, No. 3
P. 142-148

CHINESE
MEDICAL SCIENCES
JOURNAL

ORIGINAL ARTICLE

Short- and Long-term Therapeutic Efficacies of Intravenous Transplantation of Bone Marrow Stem Cells on Cardiac Function in Rats with Acute Myocardial Infarction: A Meta-analysis of Randomized Controlled Trials△

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Key words: mesenchymal stem cells; rats; myocardial infarction; intravenous

Objective To investigate the short- and long-term therapeutic efficacies of intravenous transplantation of bone marrow stem cells (MSCs) in rats with experimental myocardial infarction by meta-analysis.

Methods Randomized controlled trials were systematically searched from PubMed, Science Citation Index (SCI), Chinese journal full-text database (CJFD) up to December 2014. While the experimental groups (MSCs groups) were injected MSCs intravenously, the control groups were injected Delubecco's minimum essential medium (DMEM) or phosphate buffered saline (PBS). Subgroup analysis for each outcome measure was performed for the observing time point after the transplantation of MSCs. Weighted mean differences (WMD) and 95% confidence intervals (*CI*) were calculated for outcome parameters including ejection fraction (EF) and fractional shortening (FS), which were measured by echocardiogram after intravenous injection and analyzed by RevMan 5.2 and STATA 12.0.

Results Data from 9 studies (190 rats) were included in the meta-analysis. As compared to the control groups, the cardiac function of the experimental groups were not improved at day 7 (EF: WMD=0.08, 95%*CI* −1.32 to 1.16, *P*>0.01; FS: WMD=−0.12, 95%*CI* −0.90 to 0.65, *P*>0.01) until at day 14 after MSCs' transplantation (EF: WMD=10.79, 95%*CI* 9.16 to 12.42, *P*<0.01; FS: WMD=11.34, 95%*CI* 10.44 to 12.23, *P*<0.01), and it lasted 4 weeks or more after transplantation of MSCs (EF: WMD=13.94, 95%*CI* 12.24 to 15.64, *P*<0.01; FS: WMD=9.64, 95%*CI* 7.98 to 11.31, *P*<0.01).

Received for publication November 9, 2015.

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△Supported by the Youth Project of National Natural Science Foundation (81100078) , the Key Project of Chinese Ministry of Education (211207), Guangzhou Pearl River science and technology new star project plan (2012J2200063) and Project of Guangdong Science and Technology Department (S2011040001392).

Conclusion The therapeutic efficacies of MSCs in rats with myocardid infarction become increasing apparent as time advances since 2 weeks after injection.

Chin Med Sci J 2016; 31(3):142-148

WORLDWIDE, acute myocardial infarction (MI) is a kind of refractory and deadly disease and most will develop into congestive heart failure. It remains a major health problem, whose morbidity and mortality is still increasing despite guideline conforming pharmacological treatment and revascularization. Recently numerous experimental and clinical studies have suggested that the cell-based therapy with bone marrow stem cells (MSCs) enhanced and improved cardiac function post MI.[1-6] Mesenchymal stem cells is a type of non-hematopoietic, adult stem-like cells that can be easily isolated from the bone marrow, readily cultured and practically expanded *in vitro*. Some studies have found that MSCs could transdifferentiate into cardiomyocytes, significantly induce promoting activity of angiogenesis and myogenesis, promote neo-vascularization in infarcted hearts post MI,[3, 5, 7] while others suggested that MSCs preserved cardiac systolic and diastolic performances, improved the wall thickness of left ventricular (LV) and increased capillary density by paracrine.[6, 8-10] The specific mechanisms how MSCs enhance the cardiac function are still unclear, but it behoves us to continue to investigate a bright future for patients with acute MI.

Ejection fraction (EF) and fractional shortening (FS) calculated *via* LV end-diastolic (LVEDd) and end-systolic dimensions (LVESd) are used to estimate cardiac function and analyze the therapeutic efficacies of MSCs on cardiac function, LV EF and FS were calculated as follows: $EF=[(LVEDd^3-LVESd^3)/LVEDd^3]\times100$; $FS=(LVEDd-LVESd)/LVEDd\times100$. The normal mean value of EF is almost 84[11] and the normal mean value of FS is about 35.[12] The less scores the rats get, the worse functions they have.

This systematic review with meta-analysis in MI models by comparing the experimental groups and control groups is expected to offer an academic support for curing MI.

MATERIALS AND METHODS

Search strategy

By searching pertinent studies in PubMed, Science Citation Index (SCI), Chinese journal full-text database (CJFD) up to December 2014 we collected papers published with the keywords: "mesenchymal stem cells", "mesenchymal stromal cells", "rats", "myocardial infarction", "intravenous", "intravenously". The languages used were not restricted.

Inclusion criteria

The studies were included if they fulfilled the following criteria: (1) randomized controlled animal trials; (2) intravenous administration; (3) the parameters included EF or FS; (4) containing at least two groups: with and without intravenous transplantation of MSCs; (5) except for being injected with MSCs, the control groups got the same experimental treatment of the experimental groups; (6) acute MI models were established with rats; (7) cells used injection were extracted from rat bone marrow.

Exclusion criteria

The articles were excluded if these studies met one of the following exclusive criteria: (1) unable to get the full text; (2) the author is same with another study; (3) combined with other interventions; (4) review.

Data extraction

Two evaluators independently selected and extracted data which were collected by reading the headlines, abstracts and full texts according to the inclusion and exclusion criteria, and then reviewed those studies again before statistical analysis. We explored potential resources from the following aspects: first author's name; year of publication; the weight of rat; the number of injected cells; the route of administration; EF; FS; the observed time after MI. Disagreements were resolved by consensus.

Assessment of methodology quality

The quality of the included studies was assessed from the perspective of Cochrane Handbook for Systematic Reviews of Interventions version 5.2. There are 7 items: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. Every study was evaluated by 2 independent researchers, and the judgment of every item was at a low unclear or high risk. Disagreements were resolved by consensus.

Statistical analysis

After organizing and establishing a database, we chose the