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Review

Intramyocardial autologous bone marrow cell transplantation for ischemic heart disease: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: This study was undertaken to evaluate the efficacy of intramyocardial bone marrow cell (BMC) transplant therapy for ischemic heart disease (IHD).
Methods: The PubMed, Embase, and Cochrane Library databases through October 2013 were searched for randomized clinical trials (RCTs) of intramyocardial BMCs to treat IHD. The primary endpoint was change in left ventricular ejection fraction (LVEF). Secondary endpoints were changes in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). Weighted mean differences for the changes were estimated with a random-effects model.
Results: Eleven RCTs with 492 participants were included. Intramyocardial BMC transplantation increased LVEF (4.91%; 95% confidence interval [CI] 2.84%–6.99%; $P < 0.00001$), reduced LVESV (10.66 mL; 95% CI, −18.92 mL to −2.41 mL; $P = 0.01$), and showed a trend toward decreased LVEDV (−7.82 mL; 95% CI, −16.36 mL–0.71 mL; $P = 0.07$). Patients suitable for revascularization with coronary artery bypass grafting had greater improvement in LVEF (7.60%; 95% CI, 4.74%–10.46%, $P < 0.00001$) than those unsuitable for revascularization (3.76%; 95% CI, 2.20%–5.32%; $P < 0.00001$). LVEDV reduction was also more significant in revascularizable IHD (−16.51 mL; 95% CI, −22.05 mL to −10.07 mL; $P < 0.00001$) than non-revascularizable IHD (−0.89 mL; 95% CI, −8.44 mL–6.66 mL; $P = 0.82$).
Conclusion: Intramyocardial BMC injection contributes to improvement in left ventricular dysfunction and reduction in left ventricular volume. Patients with revascularizable IHD may benefit more from this therapy.

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1. Introduction

Ischemic heart disease (IHD) is one of the leading causes of mortality worldwide and imposes a heavy economic burden on modern society [1]. Despite major advances in pharmacological treatment and revascularization technique during the past decades, injured myocardium often dies and is replaced by scar tissue, resulting in systolic dysfunction and myocardial remodeling and, ultimately, heart failure.

Currently, stem cell transplantation is emerging as a novel strategy for myocardial regeneration and attracting the interest of researchers. Bone marrow cells (BMCs) are considered to be ideal candidates for treating myocardial injury because they are of autologous origin and readily available [2]. Since the first application of BMC therapy in myocardial infarction in 2001 [3], an increasing number of studies have been launched to evaluate its role in cardiac repair. The donor cells are transplanted into injured hearts by either an intracoronary or intramyocardial route. Initial clinical trials and meta-analyses demonstrate beneficial effects of intracoronary BMC infusion on cardiac function [4–7]. However, the efficacy of intramyocardial BMC injection remains unclear, with some studies showing favorable effects [8,9], and others indicating no benefit [10,11]. Thus, we performed this systematic review and meta-analysis to evaluate the effects of intramyocardial BMC transplantation on myocardial repair in ischemic hearts.

2. Methods

2.1. Search strategy

In accordance with Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12], the PubMed, Embase, and Cochrane Library databases through October 2013 were systematically searched for studies of intramyocardial BMC transplantation in patients with IHD. Subject terms and free text terms were used when retrieving literature from the above databases. Detailed search strategies are shown in Supplementary Tables S1–S3. The reference lists of the included studies and published meta-analyses were also hand-searched to identify other potentially relevant articles. There was no restriction on publication year or language.

2.2. Study selection

Clinical trials that met the following criteria were eligible for inclusion: (1) randomized controlled trial (RCT), (2) trial conducted in patients with IHD, and (3) autologous BMCs delivered by an intramyocardial route. Exclusion criteria were: (1) clinical trials not meeting the above criteria, (2) trials using precursors mobilized by cytokines (because cytokines may have additional effects on myocardium and BMCs), and (3) studies not reporting change in left ventricular functional parameters.

2.3. Date extraction

Two investigators (TT and YX) independently selected suitable trials and extracted data from and assessed the quality of included trials. Any discrepancies in study selection, date extraction, and quality assessment between the two investigators were resolved by discussion with a third investigator (XZ). For each study, the following information was extracted: first author, year of publication, sample size, mean age, percentage of male participants, left ventricular functional parameters, New York Heart Association (NYHA) functional class, clinical scenario, route of delivery, cell type, number of cells administered, duration of follow-up, imaging modality, and major adverse cardiovascular events.

The primary endpoint was the net change in LVEF from baseline to follow-up. Secondary endpoints included the net changes in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). For studies reporting the endpoint parameters as mean $\pm$ standard deviation (SD) at baseline and follow-up without providing the net change, the changes in mean and SD were calculated using a standardized formula proposed by the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0, the Cochrane Collaboration, 2011).

Because of the superior accuracy of magnetic resonance imaging (MRI) [13], MRI data for left ventricular functional parameters were preferentially used in the statistical analysis. Echocardiographic data were used when the MRI data were unavailable. When the outcome data were reported for multiple endpoints, six-month data were used to ensure uniformity.

2.4. Quality assessment

The assessment of methodological quality of the included RCTs was based on the criteria proposed by Juni et al. [14]. The criteria include generation of random sequence, concealment of treatment allocation schedule, blinding of patients and caregiver, blinding of outcome assessment, percentage of patients lost to follow-up, and whether all patients were treated as assigned.

2.5. Statistical analysis

Statistical analysis was performed with Review Manager (RevMan [Computer program] version 5.0; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata Statistical Software, Release 12 (StataCorp LP, College Station, TX, USA). Weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous outcomes. Heterogeneity between trials was assessed using I^2 statistics and chi-square test. The result was obtained from the random-effects model. Planned subgroup analyses were performed based on the following factors: (1) clinical scenario (revascularizable IHD vs. nonrevascularizable IHD), (2) baseline LVEF (LVEF $\geq$ 36.5% vs. $<$ 36.5% [the median baseline LVEF in the included trials was 36.5%]), and (3) imaging used to measure LVEF (MRI vs. echocardiography). Meta-regression analysis was performed to identify further the possible sources of heterogeneity and a P value of <0.1 was accepted as significant. Sensitivity analysis was performed to evaluate the robustness of the result with random-effects method. Potential publication bias was evaluated using funnel plots and the Egger and Begg tests.