Effects of stem cell therapy on left ventricular remodeling after acute myocardial infarction: a meta-analysis

Sun L, Zhang T, Lan X, Du G

CRD summary
This review concluded that evidence suggested stem cell therapy improved heart left ventricular contractibility, but had no effect on left ventricular remodelling in patients with acute myocardial infarction. Given concerns over the possibility of missed studies, the unclear quality of included data and the methods of analysis, the authors' conclusions should be treated with caution.

Authors' objectives
To assess the effects of stem cell therapy on changes in left ventricular end-diastolic volume and end-systolic volume in patients with acute myocardial infarction.

Searching
PubMed, EMBASE, the Cochrane Library, ClinicalTrials.gov and mRCT (Current Controlled Trials) databases were searched. Search terms were reported. No language restrictions were applied. Reference lists of relevant articles and reviews were checked. Only published studies were eligible for inclusion.

Study selection
Trials that compared the effects of intracoronary infusion of bone marrow cells or peripheral marrow cells versus control in people with acute myocardial infarction were eligible for inclusion. Percutaneous revascularisation of the infarct-related artery had to occur within 14 days of first symptoms of acute myocardial infarction and follow-up had to be more than three months. Trials that did not report outcomes on an intention-to-treat basis were excluded.

The primary outcomes of interest were net changes in left ventricular end-diastolic volume and net changes in left ventricular end-systolic volume.

In included studies, the mean age of participants ranged from 53 to 60 years. Most studies used bone marrow cells; some used peripheral marrow cells, with and without granulocyte colony-stimulating factor or glycoprotein CD133 plus progenitor cells. Three studies used sham injections in the control group; in other studies, the control appeared to be usual care.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
Two reviewers independently assessed the quality of included studies using items such as allocation concealment, blinding of investigators, participants and outcome assessors, use of intention-to-treat analysis, completeness of follow-up and reporting of withdrawals. A scoring system was used to summarise; available scores ranged from 1 to 5, with 5 representing better quality.

Data extraction
The mean change in left ventricular end-diastolic volume and left ventricular end-systolic volume, between baseline and follow-up were extracted. The net difference in change between treatment and control groups were calculated.

The authors did not state how many of the reviewers performed the data extraction.

Methods of synthesis
Weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated using a fixed-effect or random-effects model. Results for the fixed-effect model were reported. Heterogeneity was assessed using Cochran's Q test and
I² statistic. I² over 50% was considered to indicate significant heterogeneity between trials.

Sensitivity analyses were undertaken based on study design (RCTs versus cohort studies).

Publication bias was assessed using funnel plots and Egger's regression test.

**Results of the review**

Eleven studies (822 participants) were included in the review. Eight studies (725 participants) were randomised controlled trials (RCTs) and three studies (97 participants) were cohort studies. Quality scores ranged from 2 to 5 points. Seven studies reported adequate details of withdrawals. Follow-up for most studies was from three to six months; two studies followed up for 12 and 18 months.

Compared with control, stem cell therapy had no effect on left ventricular end-diastolic volume (11 studies; I²=1.1%), but was associated with a reduction in left ventricular end-systolic volume (WMD -5.08mL, 95% CI -7.80 to -2.37; I²=29.8%; nine studies).

In subgroup analyses, there was no significant difference in effect between results in RCTs and cohort studies.

Tests suggested that there was no evidence of publication bias.

**Authors’ conclusions**

Evidence suggested that stem cell therapy improved left ventricular contractibility, but had no effect on left ventricular remodelling.

**CRD commentary**

The aims of the review were clearly stated for participants, treatment and outcomes, but were less clear for study design. However, one of the exclusion criteria was that studies had to report on an intention-to-treat basis, but studies that did not qualify on this basis were included, and inclusion criteria for length of follow-up did not appear to be accurately reported. The search covered a number of relevant sources, including studies in any language. However, unpublished studies were excluded, so although language bias was unlikely, publication bias may have affected the review. Although tests showed no evidence of publication bias, these may have been unreliable given the limited number of included studies. Search dates were not reported, so it was not clear how up-to-date the results were. The methods of study selection and quality assessment were aimed at reducing reviewer error or bias, but it was unclear if such methods were applied to data extraction.

Study quality was assessed using items for RCT quality assessment, but these were not necessarily appropriate for observational studies; the results were reported only as a summary score, so it was not possible to distinguish between higher and lower quality studies. It may not have been appropriate to combine results from RCTs and observational studies. The authors included one study twice in the analyses (using different follow-up times); also, it was unclear how the control group were treated in a second study with two separate treatment arms. It was possible that the results were distorted because participants were represented twice in the same analyses.

Given concerns over the possibility of missed studies, the unclear quality of included data, and inappropriate methods of analysis, the authors’ conclusions should be treated with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that higher quality RCTs with longer follow-up are needed to assess the clinical effectiveness and safety of stem cell therapy in patients after acute myocardial infarction.

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