Effects of intracoronary autologous bone marrow cells on left ventricular function in acute myocardial infarction: a systematic review and meta-analysis for randomized controlled trials

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CRD summary
Intracoronary autologous bone marrow cell infusion in patients with acute myocardial infarction seemed to be safe and associated with slight improvement of the left ventricular ejection fraction at three to six months follow-up. The authors' conclusion reflects the evidence presented and is likely to be reliable.

Authors' objectives
To evaluate the effectiveness and safety of intracoronary autologous bone marrow cell therapy on global left ventricular function in patients with acute myocardial infarction.

Searching
The databases MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE and the Science Citation Index were searched from inception to March 2007. Search terms were reported. Language restrictions were not imposed, but only trials with an English description were eligible for inclusion in the review. Reference lists of identified articles, recently published editorials and relevant reviews were also searched.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) based on acute myocardial infarction standard care that compared intracoronary or transcoronary bone marrow cells infused into the infarcted areas with placebo or no placebo in patients with acute myocardial infarction. Eligible trials had to have a minimum of three to six months follow-up. Where there were multiple reports from the same trial population, only the latest trial was included in the review.

All of the following were excluded from the review: RCTs with coronary artery bypass grafting and direct intramycocardial bone marrow cell injection; bone marrow cell therapy at 18 months follow-up; RCTs with incomplete left ventricular ejection fraction data, bone marrow cells mixed with bone marrow derived stem cells, progenitor cells, or mononuclear bone marrow cell therapy (but excluding mesenchymal stem cells); blood derived progenitor cell relevant studies; and old myocardial therapy, for example, bone marrow cell infusion after three months of acute myocardial infarction.

Efficacy outcomes of interest were left ventricular ejection fraction at three to six months follow-up, and left ventricular ejection fraction change from baseline to follow-up. Adverse event outcomes were major adverse cardiovascular events, which included ventricular arrhythmia, re-hospitalisation for heart failure and the composite of other cardiovascular events (cardiac death, recurrent myocardial infarction, infarct vessel revascularisation procedure, and stroke).

Demographic characteristics of age (53.4 to 59.2 years) and sex (more than 67% male) were approximately the same for all RCTs.

Two independent reviewers selected studies for inclusion in the review. The authors did not state how disagreements were resolved.

Assessment of study quality
Trial quality was assessed using the Jadad scale. The maximum possible score was 5 points.

Two independent reviewers assessed study quality. The authors did not state how disagreements were resolved.
**Data extraction**
Data were extracted in order to calculate weighted mean differences (WMD) and risk ratios (RR), along with their 95% confidence intervals (CI).

Two independent reviewers performed the data extraction. The authors did not state how disagreements were resolved.

**Methods of synthesis**
Weighted mean differences were combined in a meta-analysis using a fixed-effect model. Heterogeneity was assessed using the Cochran Q test. Publication bias was assessed using Begg's funnel plots and the Egger's test. Sensitivity analysis was performed by excluding the subgroup with the lower dose of bone marrow cell infusion and including a trial where bone marrow cell therapy commenced at 18 months follow-up. Risk ratios were combined in a meta-analysis. For summary of risk ratios for major cardiovascular adverse events at follow-up at random-effects model was used.

**Results of the review**
Six RCTs were included in the meta-analysis (n=517 patients). Five of the trials scored 5 points, the maximum score on the Jadad scale, and one trial scored 3 points. Publication bias was reported to be absent.

Compared with control, bone marrow cell therapy caused a statistically significant improvement of the follow-up left ventricular ejection fraction (mean difference 2.53%, 95% CI 0.67 to 4.39) and of left ventricular ejection fraction change from baseline to follow-up (mean difference: 2.88%, 95% CI 1.69 to 4.08). There was no evidence of statistically significant heterogeneity. Sensitivity analysis did not significantly alter the results.

There was no statistically significant difference in the risk of major adverse cardiovascular events between control and bone marrow cell groups.

**Authors' conclusions**
Intracoronary bone marrow cell infusion in patients with acute myocardial infarction seemed to be safe and associated with slight improvement of the left ventricular ejection fraction at three to six months follow-up.

**CRD commentary**
This review addressed a clear research question and was supported by detailed inclusion criteria. The search strategy was adequate but, although no language restriction was imposed, included trials were limited to those with an English description. This meant that relevant trials could have been missed. However, publication bias was assessed and was reported to be absent. Adequate details of individual trials were provided and appropriate synthesis methods were used. However, the use of a heterogeneity assessment to determine the employment of a fixed-effect or random-effects model may not have been advisable. The review was carried out with sufficient attempts to minimise bias. Overall the authors' conclusion reflects the evidence presented and is likely to be reliable.

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

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

**Research:** The authors stated that the improvement of global left ventricular ejection fraction and regional myocardial function after dose-dependent bone marrow cell therapy in acute myocardial infarction needs to be verified in future multicentric studies.

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