Intracoronary autologous bone marrow stem cells transfer for patients with acute myocardial infarction: a meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that post percutaneous coronary intervention bone marrow stem cell transplantation in patients with acute myocardial infarction significantly increased left ventricular ejection fraction, had no effect on left ventricular remodelling, and no increase in major adverse cardiac events. The authors' conclusions represented the evidence presented, but their reliability is unclear given the presence of statistically significant between-trial variation.

Authors' objectives
To determine the efficacy and safety of autologous bone marrow stem cell transfer in patients with acute myocardial infarction.

Searching
MEDLINE, BIOSIS Previews, EMBASE, the Cochrane Database for Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), DARE, and the ACP Journal Club were searched from 1990 to 2007. The search was not restricted to English language literature. Search terms were reported. Reference lists of retrieved articles and systematic reviews were also searched.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) that compared the transfer of autologous bone marrow stem cell to percutaneous coronary intervention in combination with standard medical treatment in patients with acute myocardial infarction (as classified by the World Health Organisation Criteria) who had been successfully reperfused by stent implementation.

Trials were excluded from the review if the route of transplantation was intramyocardial injection, or if the engrafted cell type was circulating progenitor cells mobilised by granulocyte colony-stimulating factor from bone marrow.

Outcomes of interest included: left ventricular ejection fraction, left ventricular end-diastolic dimensions (measured as left ventricular end diastolic volumes in mL, left ventricular end-diastolic volume index in mL/m² or left ventricular end diastolic internal diameter in mm) and major adverse cardiac events (cumulative major cardiac events, death, ventricular arrhythmia, in-stent restenosis, and recurrent myocardial infarction).

The mean age of participants were similar in the included trials (56.0 years to 58.5 years), but the percentage of female participants varied (4 to 30%). With the exception of one trial, which used bone marrow mesenchymal stem cells, all trials used bone marrow mononuclear cells. The number of cells infused ranged from $8.71 \times 10^7$ to $24.60 \times 10^8$ for bone marrow mononuclear cells, and was $54.00 \times 10^9$ for bone marrow mesenchymal stem cells. Mean time to cell transfer after percutaneous coronary intervention also varied between trials, ranging from 0.13 to 18.4 days.

Two reviewers independently assessed studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed trial quality using the Jadad scale.

Data extraction
Data were extracted in order to calculate mean differences, standardised mean differences (SMD), relative risks (RR) and their associated 95% confidence intervals (CI).

Two reviewers independently performed data extraction using a standardised form.
Methods of synthesis
Weighted mean differences (WMDs), standardised mean differences and relative risks were combined in meta-analyses using random-effects models. Heterogeneity was assessed using the $I^2$ test. Publication bias was assessed using funnel plots.

Results of the review
Six RCTs were included in the review (525 participants). Sample sizes ranged from 20 to 204 participants. Study quality ranged from 2 to 5 points according to the Jadad scale. There was no evidence of publication bias.

Left ventricular ejection fraction
There was no statistically significant difference in left ventricular ejection fraction between the control group and bone marrow stem cell transfer group at three months. However, bone marrow stem cell transfer was associated with a statistically significant increase in left ventricular ejection fraction at six months (WMD 6.48%, 95% CI 1.59 to 11.37, four RCTs) and overall (WMD 4.77%, 95% CI 1.42 to 8.12, seven RCTs). However, there was evidence of statistically significant heterogeneity ($I^2=80.9\%$ at six months and 81.3% overall). The removal of one trial (n=69 participants), which was the only trial to use purified bone marrow mesenchymal stem cells, from the analysis resulted in the loss of between-trial heterogeneity ($I^2=0\%$) and a statistically significant difference between bone marrow stem cell and the control group at three months (WMD 2.20%, 95% CI 0.46 to 3.93). The removal of this trial did not change any of the other results.

Left ventricular end-diastolic dimensions
There was no statistically significant difference in left ventricular end-diastolic dimensions between the control group and bone marrow stem cell transfer group at three months (two RCTs), six months (three RCTs) or overall (five RCTs). There was evidence of statistically significant heterogeneity at six months ($I^2=81.4\%$) and overall ($I^2=63.5\%$). There was no statistically significant difference between the control and bone marrow stem cell transfer groups for left ventricular end-diastolic volume, left ventricular end-diastolic volume index or left ventricular end-diastolic internal diameter.

Major cardiac adverse events
There was no statistically significant difference in cumulative adverse clinical endpoints (four RCTs), death (two RCTs), ventricular arrhythmia (four RCTs), in-stent restenosis (four RCTs), or recurrent myocardial infarction (two RCT) between bone marrow stem cell transfer and control groups.

Authors’ conclusions
Post percutaneous coronary intervention bone marrow stem cell transplantation in patients with acute myocardial infarction significantly increased left ventricular ejection fraction, but had no effect on left ventricular remodelling; there was not an incremental effect in the occurrence of major adverse cardiac events in the observed period.

CRD commentary
The review addressed a clear research question and was supported by detailed inclusion criteria. The search strategy was adequate and was not limited to English language studies, reducing the risk of language bias. The review processes were carried out with sufficient attempts to minimise reviewer error and bias.

The trial quality assessment tool was appropriate for the included study design. Publication bias was also assessed and reported to be absent. Adequate details of the primary studies were provided and synthesis methods were appropriate, including attempts to explore possible sources of heterogeneity.

The authors’ conclusions represented the evidence presented, but their reliability is unclear given the presence of statistically significant heterogeneity.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that larger randomised multicentre trials with longer follow-up periods are required to attain more robust clinical evidence of myocardial cellular therapy.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.