Impact of timing on efficacy and safety of intracoronary autologous bone marrow stem cells transplantation in acute myocardial infarction: a pooled subgroup analysis of randomized controlled trials


CRD summary
The authors concluded that bone marrow stem cell transfer was superior at four to seven days post-acute myocardial infarction than within 24 hours in terms of left-ventricular ejection fraction, left ventricular end-systolic dimensions and incidence of revascularisation. However, for several outcomes there was little evidence of significant differences between subgroups and so these conclusions may not be reliable.

Authors' objectives
To assess the impact of timing on efficacy and safety of intracoronary bone marrow stem cell (BMSC) transplantation after acute myocardial infarction (AMI).

Searching
MEDLINE, BIOSIS Previews, EMBASE and The Cochrane Library were searched to identify relevant studies published between January 1990 and May 2007. Search terms were reported. Reference lists of retrieved studies were searched. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that evaluated intracoronary autologous BMSC transfer for patients admitted within 24 hours of onset of AMI were eligible for inclusion if they reported a minimum three-month's follow-up data on efficacy and safety. Studies had to use emergency percutaneous coronary intervention (PCI) and standard medical treatment without BMSC transfer as the control intervention.

In the included studies, average time to PCI ranged from 3.7 to 21.6 hours and mean time to cell transfer ranged from 0.08 to seven days after PCI.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Included studies were assessed in terms of randomisation, allocation concealment, blinding and loss to follow-up according to the 5-point Jadad quality scale.

The authors did not state how many reviewers performed the assessment.

Data extraction
Changes from baseline in terms of left ventricular end-diastolic or end-systolic dimensions (volume, volume index or diameter) and left ventricular ejection fraction (LVEF) were extracted from the included studies.

The authors stated neither how data were extracted nor how many reviewers performed extraction.

Methods of synthesis
LVEF changes from baseline were combined across studies using weighted mean differences (WMDs). Left ventricular dimensions were combined using standardised mean differences (SMDs) using random effects models. Differences in adverse event rates were presented as odds ratios (ORs) using a fixed-effect model (where heterogeneity was absent) or a random effects model (in the presence of significant statistical heterogeneity) as measured by the I² statistic.
Subgroup analyses were conducted for studies that reported cell transplantation within 24 hours post-AMI and studies that reported transplantation four to seven days after AMI. Logistic regression was used to test for treatment subgroup interactions.

Funnel plots were constructed to assess publication bias.

**Results of the review**

Seven RCTs (n=660) were included in the review. BMSC transfer was performed within 24 hours in three RCTs (n=271) and from four to seven days in four RCTs (n=389). Studies scored between 2 and 5 points on the Jadad quality scale.

Subgroup analyses indicated that BMSC transfer four to seven days post-AMI significantly improved LVEF (WMD 4.63, 95% CI 1.00 to 8.26, p=0.01) and decreased left ventricular end systolic dimensions (SMD -0.28, 95% CI -0.53 to -0.02), but not left ventricular end-diastolic dimensions. For this group, there were also observed statistically significant decreases in revascularisation (OR 0.60, 95% CI 0.37 to 0.97) cumulative deaths or recurrent myocardial infarctions (OR 0.32, 95% CI 0.11 to 0.95) and culprit artery restenosis or ventricular arrhythmia (OR 0.59, 95% CI 0.36 to 0.96). None of these outcomes were significantly different from baseline in studies that undertook BMSC transfer within 24 hours post-AMI. Only the subgroup interactions for revascularisation and combined death, recurrent myocardial infarction and revascularisation were statistically significant.

**Authors' conclusions**

BMSC transfer at four to seven days post-AMI was superior to that within 24 hours in improved LVEF, decreased left ventricular end-systolic dimensions and reduced incidence of revascularisation.

**CRD commentary**

The review question was clearly defined in terms of the participants, interventions, control groups, outcomes and study designs of interest. Attempts were made to identify all relevant evidence from a variety of sources without language restrictions. Attempts were made to minimise errors and bias in the selection of studies; it was unclear whether such efforts were made in other review processes. Statistical methods used were broadly appropriate, but it should be noted that several subgroup comparisons were based on a very limited amount of data. For most outcomes, confidence intervals for the 24-hour and four to seven day subgroup overlapped and (with the exception of revascularisation) there was little evidence of statistically significant differences between subgroups. Therefore, the authors' conclusions may not be reliable. Given the lack of studies that directly or indirectly compared early versus delayed BMSC, the authors' recommendations for further research appeared more reasonable.

**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 trials of post-AMI BMSC transfer were needed to validate the findings of this subgroup analysis.

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