Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis

CRD summary
This well-conducted review assessed the effect of bone marrow-derived cell (BMC) transplantation on cardiovascular outcomes in patients with ischaemic heart disease. The authors concluded that BMC transplantation is associated with modest improvements in physiologic and anatomic parameters compared with conventional therapy, and appears to be safe. These conclusions are likely to be reliable.

Authors’ objectives
To assess the effect of bone marrow-derived cell (BMC) transplantation on cardiovascular outcomes in patients with ischaemic heart disease (IHD).

Searching
MEDLINE, the Cochrane CENTRAL Register, EMBASE and BIOSIS Previews were searched from January 1980 to July 2006, and CINAHL was searched from January 1982 to July 2006; the search terms were reported. The authors also searched the U.S. Food and Drug Administration website and reviewed the reference lists of eligible studies and relevant review articles.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and cohort studies were eligible for inclusion.

Specific interventions included in the review
Studies of BMC transplantation were eligible for inclusion. Studies of cardiac repair solely through mobilisation of endogenous BMCs with systemic administration of cytokines were excluded. The included studies transplanted a variety of BMC populations by either intracoronary or intramyocardial injection. Studies also varied greatly in the timing of transplantation (between 1 day and 81 months after myocardial infarction (MI) or percutaneous coronary event; median 9.8 days) and the number of cells transplanted. The control interventions were not reported.

Participants included in the review
Studies of patients with IHD were eligible for inclusion. The studies in the review included participants with acute MI and/or ischaemic cardiomyopathy.

Outcomes assessed in the review
Studies reporting cardiovascular outcomes were eligible for inclusion. The outcomes assessed were: change from baseline in mean left ventricular (LV) ejection fraction; infarct scar size; and LV end-systolic volume and LV end-diastolic volume. Follow-up in the included studies ranged from 3 to 18 months (median 4).

How were decisions on the relevance of primary studies made?
Two reviewers working independently assessed the studies in duplicate.

Assessment of study quality
RCTs were assessed using the criteria of Juni et al., which consider methods of randomisation and allocation concealment, group comparability, blinding, loss to follow-up and use of intention-to-treat analysis. A modified Newcastle-Ottawa scale was used to assess cohort studies; this considers selection and comparability of cohorts, ascertainment of exposure, outcome assessment, and length and adequacy of follow-up. Two reviewers independently abstracted quality assessment data, and referred any disagreements that could not be resolved by consensus to a third reviewer.
Data extraction
Two reviewers working independently carried out the data extraction in duplicate, and referred any disagreements that could not be resolved by consensus to a third reviewer. Data were extracted on the mean difference between BMC-treated and control patients for each of the outcomes evaluated.

Methods of synthesis
How were the studies combined?
The studies were combined using random-effects meta-analyses. Weighted mean differences with 95% confidence intervals (CIs) were estimated for each outcome. Publication bias was investigated graphically using funnel plots.

How were differences between studies investigated?
Heterogeneity was investigated using the I-squared statistic and pre-planned subgroup analyses. For these analyses, the studies were grouped according to study design, clinical scenario, timing of BMC transplantation, number of cells injected and population of BMCs used.

Results of the review
Eighteen studies, with 999 participants in total, were included: 12 RCTs (830 participants) and 6 cohort studies (169 participants).

Methodological quality.
All cohort studies and 6 of the 12 RCTs failed to blind caregivers and participants; 3 of the 6 cohort studies and 2 of the 12 RCTs failed to blind outcome assessors. All studies had adequate loss to follow-up (less than 20%).

Efficacy.
BMC transplantation was associated with a significant increase in LV ejection fraction (3.66%, 95% CI: 1.93, 5.40, p<0.001; I-squared 71%), a reduction in infarct scar size (5.49%, 95% CI: -9.10, -1.88, p=0.003; I-squared 66%) and a reduction in LV end-systolic volume (4.80 mL, 95% CI: -8.20, -1.41, p=0.006; I-squared 0%) compared with control. The reduction in LV end-diastolic volume was not statistically significant (1.92 mL, 95% CI: -6.31, 2.47, p=0.39; I-squared 0%).

No treatment-subgroup interaction was found in the subgroup analyses.

Safety.
Except for 1 study reporting a higher incidence of in-stent restenosis in the BMC-treated group, the incidence of major local and systemic complications was comparable in the treatment and control groups.

Publication bias.
The funnel plots were either uninterpretable or inconclusive.

Authors' conclusions
Compared with conventional therapy, BMC transplantation is associated with modest improvements in physiologic and anatomic parameters in patients with acute MI and chronic IHD, and appears to be safe.

CRD commentary
This review addressed a clear question with defined inclusion criteria. A number of relevant sources and strategies were used in a thorough search for primary studies. Adequate steps were taken to minimise the introduction of errors and bias during the review process. The quality of the included studies was assessed using established criteria and was
considered in the analysis. Appropriate meta-analytic techniques were used to pool the results, and potentially important sources of between-study heterogeneity were investigated in subgroup analyses. This is a well-conducted review and the authors’ conclusions are 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 large RCTs should be conducted to evaluate the long-term impact of BMC therapy on patient-important outcomes in patients with IHD.

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