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A novel application of myocardial contrast echocardiography to evaluate angiogenesis by autologous bone marrow cell transplantation in chronic ischemic pig model
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OBJECTIVES: We investigated the feasibility of myocardial contrast echocardiography (MCE) to evaluate regional perfusion after bone marrow cell transplantation.
BACKGROUND: The myocardial microvessels improved by cell transplantation are too small to visualize with conventional angiography. METHODS: Fourteen mini-pigs from the Nippon Institute for Biological Science were used. The proximal left anterior descending coronary artery was ligated. One month later, nine pigs survived. Six pigs received autologous cell transplantation into the left ventricular anterior wall: bone marrow mononuclear cells (BMMNCs) (n = 3) and bone marrow stromal cells (BMSCs) (n = 3). The other three pigs received saline (control group, n = 3). The pigs were sacrificed one month later. Myocardial contrast intensity (MCI) with a contrast agent was measured using the SONOS 5500 system (Philips). Capillary density (CD) and MCI were measured at four areas: anteroseptum (nontransplanted infarct area), anterior wall (transplanted infarct area), septum (border zone), and lateral wall (normal). We compared the anteroseptum with the anterior wall by MCI and CD. RESULTS: In the BMMNC and BMSC subsets, the CD of the anterior wall was higher than that of the anteroseptum ($p < 0.001$). There was a linear relation between MCI and CD (acoustic unit [AU2] = 0.234 CD + 0.010, $r = 0.92$, $p < 0.001$). At one month after cell transplantation, MCI of the anterior wall increased in the BMMNC and BMSC subsets ($p < 0.05$), although it did not change in the control group. The ratio of wall thickness (systole/diastole) in the transplanted infarct area was larger than that in the nontransplanted infarct area ($p < 0.01$). CONCLUSIONS: Myocardial contrast echocardiography is useful to evaluate regional perfusion, which was enhanced by bone marrow cell transplantation.
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Lancet (2004);363:751-6
Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial
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BACKGROUND: Bone-marrow stem-cell transplantation has been shown to improve cardiac function in patients with myocardial infarction. We examined the feasibility and efficacy of granulocyte-colony stimulating factor (G-CSF) therapy and subsequent intracoronary infusion of collected peripheral blood stem-cells (PBSCs) in such patients.
METHODS: We prospectively randomised 27 patients with myocardial infarction who underwent coronary stenting for the culprit lesion of infarction into three groups; cell infusion (n=10), G-CSF alone (n=10), and control group (n=7). Changes in left ventricular systolic function and perfusion were assessed after 6 months. By December, 2003, seven patients from the cell infusion group, three from the G-CSF group, and one

from the control group had been assessed. FINDINGS: G-CSF injection and intracoronary infusion of the mobilised PBSC did not aggravate inflammation and ischaemia during the periprocedural period. Exercise capacity (mean treadmill exercise time: 450 s [SD 178] at baseline vs 578 s [168] at 6 months' follow-up, p=0.004), myocardial perfusion (perfusion defect 11.6% [9.6] vs 5.3% [5.0], p=0.020) and systolic function (left ventricular ejection fraction 48.7% [8.3] vs 55.1% [7.4], p=0.005) improved significantly in patients who received cell infusion. However, we noted an unexpectedly high rate of in-stent restenosis at culprit lesion in patients who received G-CSF, and therefore we stopped enrollment. INTERPRETATION: G-CSF therapy with intracoronary infusion of PBSC showed improved cardiac function, and promoted angiogenesis in patients with myocardial infarction. However, aggravation of restenosis could be a serious problem. In future studies with G-CSF based stem-cell therapy, patients should be carefully monitored for unexpected effects.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15016484

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Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy
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BACKGROUND: We recently reported the safety and feasibility of autologous bone marrow mononuclear cell (ABMMNC) injection into areas of ischemic myocardium in

dogs
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Mesenchymal stromal cells (MSCs) have the potential to treat many myocardial diseases. We investigated whether these multipotent stem cells derived from bone marrow could be administered safely into the coronary circulation of healthy dogs. We injected about 0.5 million cells per kg bodyweight of early passage autologous MSCs into the left circumflex coronary artery of anaesthetised dogs. During administration, we noted ST segment elevation and T wave changes characteristic of acute myocardial ischaemia. 7 days later, macroscopic and microscopic evidence of myocardial infarction was noted. Histological sections of myocardium showed several scattered regions of dense fibroplasia accompanied by macrophage infiltrates only in areas where the MSCs were observed. We also noted raised plasma concentrations of cardiac troponin I and collagen fibril deposition in the lesions. These findings show acute myocardial ischaemia and subacute myocardial microinfarction after intracoronary arterial injection of MSCs into dogs.
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Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial
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BACKGROUND: Emerging evidence suggests that stem cells and progenitor cells derived from bone marrow can be used to improve cardiac function in patients after acute myocardial infarction. In this randomised trial, we aimed to assess whether intracoronary transfer of autologous bone-marrow cells could improve global left-ventricular ejection fraction (LVEF) at 6 months' follow-up. METHODS: After successful percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction, 60 patients were randomly assigned to either a control group (n=30) that received optimum postinfarction medical treatment, or a bone-marrow-cell group (n=30) that received optimum medical treatment and intracoronary transfer of autologous bone-marrow cells 4.8 days (SD 1.3) after PCI. Primary endpoint was global left-ventricular ejection fraction (LVEF) change from baseline to 6 months' follow-up, as

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Unexpected severe calcification after transplantation of bone marrow cells in acute myocardial infarction
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BACKGROUND: There has been a rapid increase in the number of clinical trials using unselected bone marrow (BM) cells or the mononuclear fraction of BM cells for treating ischemic heart diseases. Thus far, no significant deleterious effects or complications have been reported in any studies using BM-derived cells for treatment of various cardiac diseases. METHODS AND RESULTS: Seven-week-old female Fisher-344 rats underwent surgery to induce acute myocardial infarction and were randomized into 3 groups of 16 rats, each receiving intramyocardial injection of either 7x10(5) DiI-labeled total BM cells (TBMCs), the same number of DiI-labeled, clonally expanded BM multipotent stem cells, or the same volume of phosphate-buffered saline in the peri-infarct area. Echocardiography 2 weeks after cell transplantation indicated intramyocardial calcification in 4 of 14 surviving rats (28.5%) in the TBMC group. Histological examination with hematoxylin and eosin staining and von Kossa staining confirmed the presence of extensive intramyocardial calcification. Alkaline phosphatase staining revealed strong positivity surrounding the calcified area suggestive of ongoing osteogenic activity. Fluorescent microscopic examination revealed that acellular calcific areas were surrounded by DiI-labeled TBMCs, suggesting the direct involvement of transplanted TBMCs in myocardial calcification. In contrast, in hearts receiving equal volumes of saline or BM multipotent stem cells delivered in the same manner, there was no evidence of calcification. CONCLUSIONS: These results demonstrate that direct transplantation of unselected BM cells into the acutely infarcted myocardium may induce significant intramyocardial calcification.
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