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Autologous bone marrow mononuclear cell transplantation in ischemic heart failure: A prospective, controlled, randomized, double-blind study of cell transplantation combined with coronary bypass

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KEYWORDS:
myocardial infarction;
heart failure;
bypass surgery;
bone marrow mononuclear cells;
cell therapy;
clinical trial

BACKGROUND: Bone marrow mononuclear cell (BMMC) transplantation for heart failure has shown inconsistent therapeutic efficacy.

METHODS: We enrolled 104 ischemic heart failure patients scheduled for coronary artery bypass surgery (CABG). After 4- to 12-week pharmacotherapy optimization, 39 patients with left ventricular ejection fraction (LVEF) of ≤45% received injections of BMMC or vehicle intra-operatively into the myocardial infarction border area in a randomized, double-blind manner.

RESULTS: The median number of cells injected was 8.4×10^8 (interquartile range [IQR]: 5.2×10^8 to 13.5×10^8). We measured LV function and myocardial scar size by magnetic resonance imaging (MRI), and viability by positron emission tomography (PET) and single-photon emission computed tomography (SPECT), pre-operatively and after 1-year follow-up. LVEF, the pre-defined primary end-point measure, improved by a median of 5.6% in the control group (IQR 0.2 to 10.1) and by 4.8% in the BMMC group (IQR −0.5 to 8.2) ($p = 0.59$). Wall thickening in injected segments rose by a median of 4.5% among controls (IQR −18.1 to 23.9) and by 5.5% in the BMMC group (IQR −6.6 to 26.5) ($p = 0.68$). Changes in viability by PET and SPECT did not differ between groups. Myocardial scar size by MRI in injected segments rose by a median of 5.1% among controls (IQR −3.3 to 10.8), but fell by 13.1% in the BMMC group (IQR −21.4 to −6.5) ($p = 0.0002$).

CONCLUSIONS: BMMC therapy combined with CABG failed to improve LV systolic function, or viability, despite reducing myocardial scar size.

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Cell transplantation as a regenerative modality for ischemic heart disease has been studied for about a decade. In experimental studies, bone marrow–derived cell transplantation has

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been shown to improve left ventricular function and diminish infarct size.[1,2] Clinical trials have struggled to demonstrate this effect due to variations in or even lack of a placebo group; methods for evaluating therapeutic efficacy also vary. Moreover, in published studies, medical treatment has not been standardized. Nevertheless, treatment with non-cultured and unfractionated bone marrow mononuclear cells (BMMCs) is considered safe, and some clinical trials have suggested that BMMC transplantation also improves global left ventricular (LV) systolic function.[3–6]

We set out to distinguish the effect of BMMCs from background influences related to bone marrow aspiration, cell-delivery vehicle or intramyocardial injection. After optimization of the current standard pharmacotherapy, only patients still meeting the entry criteria were randomized to receive either placebo or BMMCs during elective coronary artery bypass surgery (CABG). We evaluated cardiac parameters by magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET), before intervention and at 1-year follow-up.

Methods

Patient selection

Patients of either gender evaluated in our cardiovascular laboratory and scheduled for CABG with moderate heart failure were eligible if meeting the inclusion criteria (Table 1).

Baseline investigation and randomization

Eligible patients received optimal pre-operative medication for heart failure and coronary disease, including at least two heart failure drugs at the highest tolerated dose. These were an angiotensin-converting enzyme inhibitor (ACE-I), or angiotensin II receptor blocker (ARB), or a beta-blocker, or a combination together with diuretics or an aldosterone antagonist. Coronary medication was a statin and anti-coagulation, aspirin or clopidogrel. After 4- to 12-week drug optimization, the screening echocardiogram was repeated. Left ventricular ejection fraction (LVEF) of $\leq$45% meant the patient could be included after informed consent. After inclusion, CABG was scheduled with baseline studies performed during the waiting period. Approval was granted by the institutional ethics committee (Dn:o HUS 456/E6/05).

Before examination, numbered randomization envelopes were sealed by stem-cell laboratory personnel blinded to other participants. After delivery of the bone marrow harvest to the stem cell laboratory, randomization of each patient was done at time of operation.

Table 1 Criteria for Eligibility

Inclusion criteria
1. Age between 18 and 75 years
2. Informed consent obtained
3. LVEF between $\leq$45% and $\geq$15%
4. NYHA Class II–IV heart failure symptoms
Exclusion criteria
1. Heart failure due to LV outflow tract obstruction
2. History of life-threatening ventricular arrhythmias or resuscitation, a condition possibly repeating, or an implantable cardioverter-defibrillator
3. Stroke or other disabling condition within 3 months before screening
4. Severe valve disease or scheduled valve surgery
5. Other disease limiting life expectancy
6. Contraindications for coronary angiogram or MRI
7. Participation in some other clinical trial

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Harvest, processing and masking of bone marrow aspirate

After anesthesia induction, 100 ml of bone marrow aspirated from each patient's posterior iliac crests was collected into a sterile bag containing heparin (final concentration 20 units/ml). The aliquots were filtered and density-gradient centrifuged (Ficoll-Paque Premium; GE Healthcare Bio-Sciences Ab, Uppsala, Sweden; Cobe 2991 Cell Processing Centrifuge, Caridian BCT) to obtain the mononuclear cell fraction, according to standard methods in use at the Meilahti Hospital Stem Cell Laboratory, Helsinki University Central Hospital. The cells were washed with medium 199 containing human serum albumin 0.5% and heparin (20 units/ml), and finally suspended in 6 ml, in the same medium. The cell suspension was divided into six 1-ml syringes for each treatment-group patient. Controls received only vehicle medium by syringes. Treatments were masked by covering syringes with non-transparent tape.

Cell counts and flow cytometry for CD34, CD117, CD133 and CD19 of the bone marrow harvest were performed for the treatment group using standard methods from the clinical flow cytometry laboratory and FACSCalibur (Becton-Dickinson, San Jose, CA). Monoclonal antibodies were from Becton-Dickinson, except for CD133 (Miltenyi Biotech, Auburn, CA).

Operation and transplantation procedure

After bone marrow aspiration, standard CABG operation was performed under cardiac arrest, cardiopulmonary bypass (CPB), cardioplegia protection and mild hypothermia. After completion of bypass anastomoses, each patient received, under cardiac arrest, 15 to 20 0.2-ml injections into the infarction border area through a small 24G needle into sites chosen before surgery by using imaging data. Injection procedure was carefully photographed during each surgery, and segments injected were specified in patients' documentation for analysis.

End-point measures

The primary end-point was change in LVEF after 1-year follow-up, as measured by magnetic resonance imaging (MRI). Secondary end-points were: changes in any other cardiac parameters as measured by MRI; ischemia area measured by PET; plasma concentrations of pro–B-type amino-terminal natriuretic peptide (proBNP); and hospitalization or the days in hospital, all compared between groups. MRI, PET, and SPECT were performed 1 week before and 1 year after surgery. Clinical evaluation and proBNP measurement were done pre-operatively and 1 year post-operatively.

Cardiac MRI

MRI was performed with a 1.5-T Sonata scanner and phase-array cardiac coil (Sonata; Siemens AG, Erlangen, Germany). Images

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