Original Article

Autologous bone marrow stem cell transplant in acute myocardial infarction

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Abstract

Objective: To evaluate the effects of autologous bone marrow stem cell transplant on clinical symptoms, overall left ventricle ejection fraction and myocardial perfusion in patients with recent anterior myocardial infarction in left anterior descending artery territory.

Methods: The study was conducted in the department of interventional cardiology of Armed Forces Institute of Cardiology, National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi from June 2004 to November 2006. There were 26 male patients with recent anterior myocardial infarction, having anterior/apical hypokinesia and disease process involving only left anterior descending artery, who were recruited. The whole procedure was explained to the patients in the language of their best understanding and informed consent was obtained. Stem cell harvest was obtained from both posterior superior iliac crests, which were processed to note total and mean mononuclear cell counts. Stem cells were transplanted into the damaged myocardium using stop flow technique through lumen of over-the-wire balloon catheter, placed in mid left anterior descending artery.

All patients tolerated the procedure well except for a few complications which were tackled by the experienced operators. The patients were advised to continue conventional medical therapy. The efficacy of stem cell transplant was objectively assessed by comparing effects on three parameters — clinical, left ventricle cineangiographic, and nuclear scintigraphic status — at baseline and at 12 weeks after transplantation.

Results: There is improvement in general well being, left ventricle ejection fraction and myocardial perfusion after stem cell therapy.

Conclusion: Autologous bone marrow stem cell transplant seems to be a favourable and secure way of treatment for improvement of post-myocardial infarction ejection fraction and perfusion. There is dire need to conduct larger randomised controlled trials to assess efficacy of this cost-effective mode of therapy, especially in our part of the world.

Keywords: Autologous Bone Marrow Stem Cells, Ejection Fraction, Anterior Myocardial Infarction, Myocardial Perfusion Scan (JPMA 62: 2; 2012).

Introduction

Cardiovascular disease is the major cause of death throughout the world. Acute myocardial infarction and consequent heart failure is the major factor of mortality and morbidity worldwide.[1] There is progressive left ventricle dilatation and systolic dysfunction as a result of remodeling of myocardium following myocardial infarction.[2]

There are certain factors that necessitate exploration of new therapeutic modalities for long-term management of post-myocardial infarction heart disease. One of this is the inability of all the available treatment options to repair and replace infarcted segment and prevent progressive left ventricle remodeling and systolic dysfunction. The other is socioeconomic burden both on individual and society as a result of time and economic loss due to post-infarction failure. Stem cell transplantation can result in myocardial regeneration by halting the detrimental haemodynamic and neuroharmonal effects that result in post-infarction heart failure.[3]

The main aim of the study was to document the effects of bone marrow stem cell transplantation on clinical symptoms, overall ejection fraction and myocardial perfusion in young patients with recent anterior myocardial infarction.

Patients and Methods

Twentysix male patients, mostly serving soldiers (mean age 35 ± 6 years), with recent anterior myocardial infarction (18 ± 5 days) were randomly recruited in the study. The whole procedure was explained to the patients in the language of their best understanding and informed consent was obtained. The study protocol was approved by the hospital's ethical committee. Coronary angiography was performed. Patients having focal anterior/apical hypokinesia and disease process involving only left anterior descending (LAD) artery were included in the study. Those (n-9) having lesions amenable to angioplasty, underwent intervention to LAD. The ones having double/triple vessel coronary artery disease and generalized LV hypokinesia were excluded from study (Table-1).

Table-1: Main angiographic findings.

Recanalised LAD	17
Occlusive LAD disease	09
Thrombus in LMS	01
LV Clot	02

LAD: Left Anterior Descending Artery; LMS: Left Main Stem; LV: Left Ventricle.

Baseline parameters of all patients were recorded that included assessment of clinical symptoms/general wellbeing using the Visual Analog Scale (VAS) score, and LV ejection fraction and geometry using LV cineangiogram performed under standardised condition i.e. in Right Anterior Oblique (RAO) 30° and Left Anterior Oblique (LAO) 50° projections. The same amount of dye 30/15 cc was used in all the patients with the help of power injector. Some of the patients underwent assessment of LV function by Technetium MIBI (Methoxy Iso Butyl Isonitrile) scan after Adenosine stress.

Stem cell harvest was obtained by 10-15 aspirations at three levels from both posterior iliac crests under aseptic conditions. It was stored in a bag containing CPD-A (Citrate Phosphate Dextrose-Adenine) as an anticoagulant and preservative after passing twice through mircofilters. The bone marrow harvest was centrifuged and total leukocyte [(mean ±SD) x 10[³]/μ L - 23.54±7.47], total mononuclear cells [(mean ± SD) percentage - 45.69±6.12] and mean mononuclear cell counts [(mean +SD) x10 /kg - 14.75+14.56] were determined.

All patients underwent left heart catheterisation via femoral arterial access. The procedure began by performing LV cineangiogram in RAO 30° & LAO 50° projections to document basal LV function. Then a standard 6 French coronary angioplasty guiding catheter was placed to the ostium of the left coronary artery and a soft-tip intracoronary guide wire was introduced to the distal segment of the LAD. The use of antithrombotic, including the dose of periprocedural unfractionated heparin, was exactly the same as during any other Percutaneous Coronary Intervention (PCI) procedure. Until this point, the procedure was exactly the same as any routine coronary angioplasty.

During intracoronary artery infusion, cells were delivered to the heart via a short over-the-wire balloon catheter (Usually 2 ×10 mm with central lumen, Sprinter-Medtronic), which was placed in mid-LAD above the border zone of the infarction. During repeated (up to six) low-pressure balloon inflations (lasting up to 3 min), the bone marrow stem cells were slowly and softly injected through the central lumen of the balloon catheter in a total volume up to 40-50 ml. The balloon remained inflated for 3 minutes in order to increase the time of contact of stem cells with the microcirculation of the infarct-related artery. The coronary artery was re-perfused after every dose of cells for 3 minutes, and therefore the total duration of procedure was about 45-60 minutes. The procedure was finished by controlled coronary angiography to show unchanged morphology and flow in the treated vessel. During the procedure the patients were monitored for chest pain, haemodynamic instability and rhythm changes. After the procedure, the patients were continually ECG-monitored for 18-24 hours and cardiac enzymes were checked twice at 12-24 hour intervals. They were managed as per post-PCI protocol and were advised to continue standard medical therapy and have fortnightly followups.

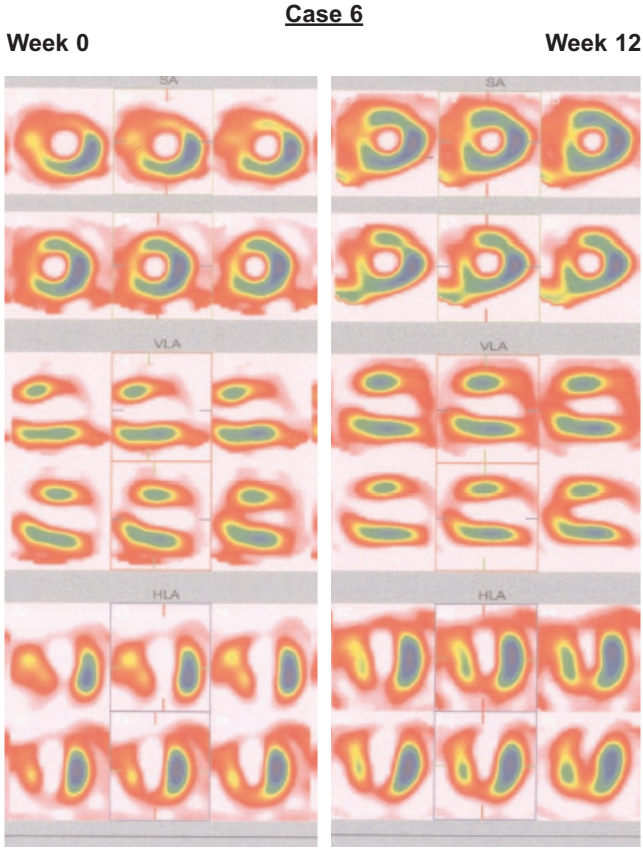
The patients were re-assessed after 12 weeks of stem

cell transplantation They were assessed clinically for improvement in symptoms and general wellbeing using VAS score, angiographically for augmentation in ejection fraction/recovery of wall motion abnormalities, and nuclear scintigraphically for enhancement in myocardial perfusion. LV systolic and diastolic contours were outlined and superimposed to calculate ejection fraction with the help of software provided by Siemens Hi cor Top. The baseline and final parameters were compared using standard software provided by Siemens Hi cor Top and Gated Spect respectively. So far, 16 patients in LV cineangiogram and 10 patients in nuclear MIBI scan arm have been studied. The data was statistically analysed by using SPSS version 10.

All patients tolerated the procedure well. Some experienced procedural events like LAD spasm (2 cases), chest pain with transient distal LAD occlusion (1 case), transient chest pain and ST/T depression during balloon inflation/stem cell infusion (5 cases), cardiac arrest (1 case), LV thrombus (2 cases), Bradycardia (2 cases), atrial and ventricular ectopic (2 cases) and ventricular tachycardia (2 cases). All procedure-related events were managed aggressively by the experienced operators.

Results

After twelve weeks of stem cell transplant, clinically there was improvement in symptoms and general wellbeing from VAS score of 2 to 8. LV cine showed improvement in ejection fraction from 40 to 46% in RAO 30° projection (p 0.01); from 57 to 60 % in LAO 50° view (p-ns) (Table-2). Myocardial MIBI scan revealed significant improvement in myocardial perfusion in six cases, moderate in two and no improvement in two cases (Figure).



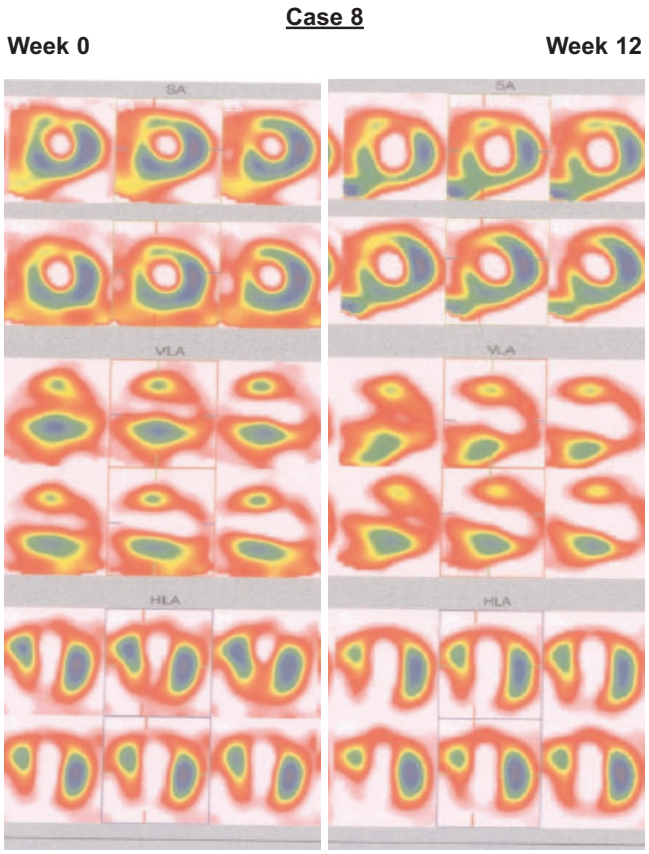


Figure: Nuclear MIBI scan showing improvement in myocardial perfusion in anterior wall in Case 6 and no improvement in Case 8.

Table-2: LV Cineangiogram data depicting enhancement in EF in RAO 30° view (n=16).

	Week 0	Week 12	P
RAO 30° view	40±4	46.39±6	0.010
LAO 50° view	57±5	60.75±7	NS

RAO: Right Anterior Oblique; LAO: Left Anterior Oblique.

Discussion

The fact that some cardiomyocytes have the ability to divide by re-entering into cell cycle following death of myocytes as a result of acute myocardial infarction has been received with great enthusiasm.[4] Another milestone is documentation of extramedullary haematopoiesis in four

patients following acute myocardial infarction by Goldman and Wurzel.[5]

Hence demonstration of extramedullary haematopoiesis and inability of current pharmacotherapy in preventing post-infarction LV remodelling coupled with ongoing optimistic research work in regenerative medicine using stem cells have encouraged researchers all over the globe to work on this new exciting treatment modality for the prevention of the ever increasing disease entity i.e. post-infarction heart failure. Stem cells are immature, undifferentiated precursor cells that have the capacity to proliferate for indefinite periods in culture and to differentiate into one or more types of specialised cells.[6]

The Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI)[7] study recruited 20 patients who underwent primary angioplasty and stenting and were given intracoronary infusion of both types of cells i.e. circulatory and bone marrow derived progenitor cells unlike in our study where we used bone marrow derived progenitor cells alone. They used LV cineangeography and MRI for assessment of LV function following stem cell therapy, showing that the transplantation of both circulating blood-derived and bone marrow-derived progenitor cells had favourable effects on post-infarction left ventricular remodelling process, regional contractile function of the infarct zone, and coronary blood flow reserve in the infarct-related artery.

Strauer et al[8] administered bone marrow stem cells in ten patients, 5-9 days after acute myocardial infarction via the intracoronary route like our study. Pre- and post-procedure assessment of LV function was carried out by LV cineangiography and nuclear scintigraphy like in our study. The area of infarction decreased notably and heart function recovered to a great extent over a period of 3 months without any significant untoward effects.

The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST)[9] study was one of the first randomised, controlled studies of stem-cell transplantation in patients with acute myocardial infarction. Cardiac MRI was used to assess the improvement in LVEF in contrast to nuclear perfusion scan in our study.

These trials have revealed that there is slight enhancement of myocardial perfusion and function at 3 to 6 months without any significant adverse effects. The salutary effects of progenitor cell transplantation persisted during a 1-year follow-up period without significant untoward events in TOPCARE-AMI trial.[10] However, no significant differences between patient and control groups regarding improvement of cardiac functions were reported at 18 months' follow-up of BOOST trial.[11]

In the REPAIR-AMI, a randomised, double-blind, placebo-controlled trial, 204 patients with acute myocardial infarction were randomly assigned to receive an intracoronary infusion of progenitor cells derived from bone marrow or placebo into the infarct artery 3 to 7 days after successful reperfusion therapy. The absolute improvement in global left ventricular ejection fraction (LVEF) at four months was significantly greater in the bone marrow-derived progenitor cell group than in the placebo group.[12] At 1 year, intracoronary infusion of bone marrow-derived progenitor cells was associated with a reduction in the predetermined combined clinical end point of death, recurrence of myocardial infarction, and any revascularisation procedure.[13] Contrary to these results, another recently published randomised study — ASTAMI trial — showed no effects of intracoronary injection of autologous mononuclear bone marrow-derived progenitor cells on global left ventricular function during 6-month followup period.[14]

In all the above mentioned trials, intracoronary route of stem cell administration was used like in our study. Selective intracoronary injection delivers an optimal number of cells evenly to the site of injury.[15] It has been suggested that smooth and equal distribution of stem cells through this route results in the absence of arrhythmias after intracoronary injection. Such injections using an over-the-wire balloon catheter are considered a safe mode of delivery of the stem cells.[9]

The study has several limitations. There is no control group and moreover the number of patients who underwent the procedure is quite low in order to infer a statistically significant conclusion for clinical application. The improvement in clinical symptoms as judged by VAS scale can well be a matter of time lag after the acute event, but none of the patients experienced gradually worsening myocardial dysfunction. One can have a biased opinion and individual variations while evaluating improvement in clinical symptoms and LV ejection fraction by cineangiogram, but documenting post-stem cell transplant enhancement of myocardial perfusion as evident on nuclear MIBI scan is a reasonably significant proof of beneficial effects of stem cell transplantation in cases of acute myocardial infarction. Concomitant percutaneous or surgical revascularisation makes the effectiveness of stem cell therapy difficult to assess. Medium and long-term outcome of these patients are not available.

Conclusion

In spite of its limitations, the study has reasonable ground to conclude that cardiac stem cell transplantation appears a promising and safe mode of therapy for the enhancement of post-myocardial infarction ejection fraction and perfusion. Whether stem cell transplantation offers a sustained clinical benefit by reversing ventricular remodelling in myocardial infarction is unknown, given that too few patients have undergone stem cell transplantation to derive any meaningful efficacy and safety data. At present, stem cell

therapy cannot be regarded as a valid therapeutic option for patients with cardiovascular disease in the present era of evidenced-based medicine. Larger double-blinded, controlled studies with therapeutic end points are necessary to clarify the short and long-term effects of myocardial cellular therapy and suitability for clinical application.

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