

Transcatheter Autologous Bone Marrow Cells in Chronic Myocardial Infarction using Helical Needle Catheter, Two Year Follow-up in an Open-Label, Non-Randomized, Single-Center Pilot Study (the TABMMI study)- A First in Man Cell Therapy Trial with new delivery Catheter Technology

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Abstract:

Background: Helical needle fixation has promise as an enabling platform for clinical cell therapy that may be implemented with fluoroscopic guidance. We assessed the hypothesis that helical needle transcatheter delivery of autologous bone marrow (ABM) mononuclear cells around regions of hypo or akinesia in chronic post-myocardial infarction (MI) patients would be safe and possibly improve ejection fraction (EF). **Methods:** 17 stable post-MI ischemic heart failure patients with an EF <40% were enrolled. ABM cells were aspirated from the iliac crest, washed, filtered, counted for CD34+ and CD133+ content, resuspended at a concentration of 100 million cells/cc, and delivered to the heart percutaneously from 5 to 10 approximate peri infarct sites with a transcatheter helical needle catheter and steerable Morph guide catheter platform. 2D echo left ventricle EF measurements, 24 hour Holter, and exercise tolerance testing were performed at baseline, day of procedure, 1 and 12 weeks, 6, 12, and 24 months. **Results:** An average of 92 million ABM mononuclear cells were injected into 8.1±2.9 sites around the infarct to target the peri-infarct zones (n=17). There were no adverse events associated with the catheter based cell transplantation procedure in any of 17 patients treated to date. There has been no significant increase in the averaged number of ventricular events on 24h Holter. In patients with 2 year follow-up (n=10), EF significantly increased over baseline (35.2±4.6 %) at each time point: 6 months (40.8±4.5, p=0.003), 12 months (42.3±5.1, p=0.0001) and 24 months (42.3 ±6.1, p = 0.0008). The average end diastolic ventricular dimension and exercise tolerance trended toward benefit, but differences were not statistically significant. **Conclusions:** ABM cells delivery with the helical needle transcatheter catheter was safe in this small uncontrolled study in patients with chronic MI. Increased ejection fraction and other positive data trends support continued development of this therapeutic strategy in larger controlled trials.

Methods:

Population Studied

Patients were enrolled who had sustained a transmural myocardial infarction and showed echocardiographic evidence of left ventricular dysfunction having ejection fractions of <40%.

Marrow Harvest and Processing

Approximately four hours prior to the percutaneous catheterization, 50 cc of autologous bone marrow cells were collected under local anesthesia from the posterior iliac crest. Bone marrow mononuclear cells were isolated by density gradient on Ficoll-Paque Plus tubes (Amersham Biosciences). Cells were washed and filtered through 100 µm nylon mesh to remove cell aggregates, and resuspended in Ringers solution at a concentration of 1 x 10⁸ cells/ml in a total volume of 1.3 ml. 10% of the final cell solution was used for cell counting and viability testing using trypan blue exclusion. Enumeration of CD34+ and CD133+/+ cells was done by the standards proposed by International Society of Hematology and Graft Engineering.

Catheter Delivery of Cells

Prior to cell delivery, the infarct target zones were defined using ECG, baseline echocardiography, and previous orthogonal ventriculography data. Upon catheterization, the selected target regions were assessed using fluoroscopy. Three investigators established anatomic consensus regarding the helical needle placement in predefined target regions. Cells were delivered transcatheterially with the two-catheter Helix Infusion System for transcatheterial delivery (BioCardia, Inc., South San Francisco, CA).

| Test or procedure | Baseline | Trans-plant | Follow-up visit windows: | | | | | | | |
|----------------------------|----------|-------------|--------------------------|--------------------------|----|-----|----|-----|-----|---|
| | | | Weekly visits (±3 days) | Monthly visits (±7 days) | W1 | W12 | M6 | M12 | M24 | |
| ABM Aspiration | | X | | | | | | | | |
| Cell Implantation | | X | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X |
| ECG | X | | X | X | X | X | X | X | X | X |
| Echo | X | X | | X | X | X | X | X | X | X |
| 24 Hour Holter | X | | X | X | X | X | X | X | X | X |
| Exercise Tolerance Testing | X | | | X | X | X | X | X | X | X |
| Blood Tests | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X |
| Concomitant Meds | X | X | X | X | X | X | X | X | X | X |

Figure 1. Delivery through helical needle catheter from within the heart

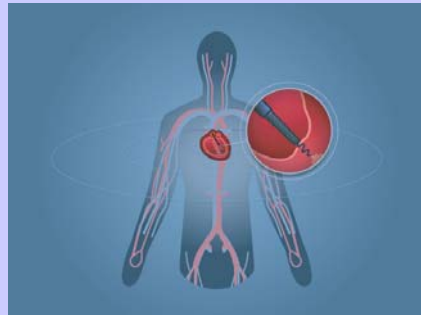


Figure 2. The Helix catheter for transcatheterial delivery is advanced through a steerable guide (not shown). In addition to the therapeutic lumen which discharges at the distal tip of the helix, it has a second lumen which discharges from the base of the helix for delivering contrast to confirm engagement and positioning.

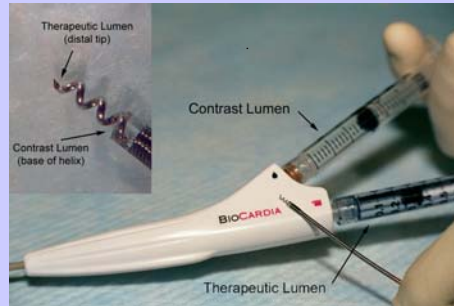


Figure 3. Cine image of the Helix catheter system showing contrast discharged at the Helix base to confirm engagement with the endocardium.

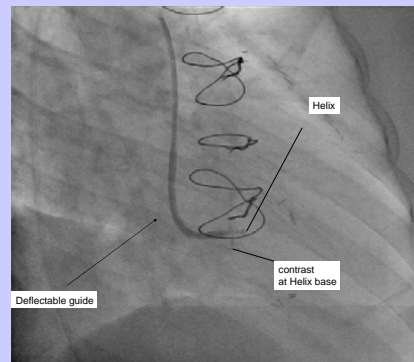


Figure 4: Ventricular Events on 24 Hour Holter. There are no statistical differences in these values. Error bars denote ± stdev.

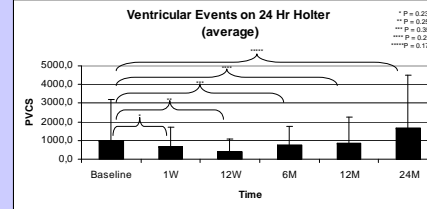


Figure 5: Changes in ETT are not statistically significant. Error bars denote ± stdev.

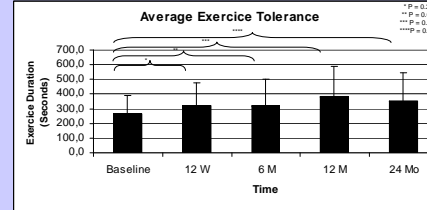


Figure 6: Changes in ejection fraction at 12 W, 6M, 12M and 24M are statistically significant. Error bars denote ± stdev

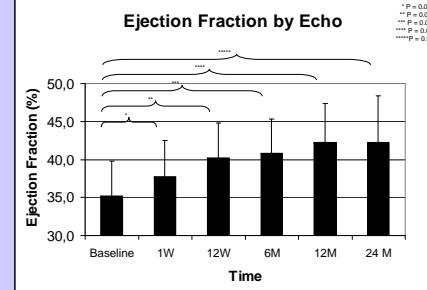
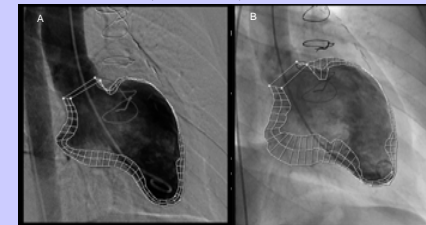


Figure 7: Right anterior oblique left ventriculogram on date of procedure (A) and at 6 month follow-up (B) showing ejection fraction (EF) changing from 37.9% to 50.1%, respectively. It should be noted that on echo this patient had an ejection fraction of 39% at baseline and 46% at 6 Month follow-up. A. End Systolic Volume (ESV) 81.9 ml, End Diastolic Volume (EDV) 131.8 ml, EF 37.9%. B. ESV: 92 ml, EDV 184.4 ml, EF: 50.1%.



Discussion:

The patients were selected to provide a stable data set by the chronic unchanging nature of their LV dysfunction, and the absence of other clinical parameters that could account for late improvement. Further, the stable chronic infarct population with ejection fractions between 30 to 40% represent the subset for whom the advancement to congestive heart failure is a common progression.

One primary safety issue for cell therapy strategies is the potential to cause cardiac arrhythmias. The Holter measurements suggest that there are no arrhythmia safety issues within 24 months of such a procedure, although the presence of an episode of ventricular tachyarrhythmia warranting implantation of an AICD at 11 months in one patient is noted. This individual at baseline had an ejection fraction of less than 35% and would have warranted an AICD based on the recent MADIT II and SCD-HEFT trials. This patient did not demonstrate any significant Holter detected arrhythmias at baseline or follow-up, and the AICD has not noted any evidence of sustained VT or discharges since implantation.

The transthoracic echo measurements of ejection fraction demonstrate improvements in all patients at 24 months in this pilot study. However, it is noted that one patient had a precipitous fall in ejection fraction from baseline to 3 months and that this significant change reversed itself. These unpredicted improvements in EF at 24 months are not powered to confirm the clinical efficacy of this therapy but they are compelling in a safety pilot trial. In this regard, the echo measurements of end diastolic volume also trended downward, suggesting overall anatomic LV improvements despite the lack of statistical power. Baseline and follow up echocardiographies were performed by the same technician operator.

By using the helical fixation transcatheterial delivery device, the investigators were provided with a means to target segmental dyskinesia with stability from myocardial fixation during the delivery process. This enables physician-operators to agree on the delivery location as well as to control the time course of delivery. The helix fixation needle may reduce back-leak into the ventricular chamber by providing a simplified direct means to confirm that one is positioned within the myocardium, a longer self sealing helical pathway into the tissue, and the ability to leave the helix in place after delivery to act as a barrier to obstruct backleak.

The obstruction of backleak may be extremely important if cells or cell aggregates do have the ability to act as microemboli. Care in cell processing to ensure that cell aggregates are not present may mitigate this issue. However, backleak may also be important should future strategies seek to incorporate other more viscous materials to enhance retention.

By selecting stable patients for this sole therapy safety study we maximized the signal to noise ratio associated with any damage or detriment to the patients treated. This was not intended to be an efficacy study, and the improvements in functional measures observed may be due to other clinical realities that results from frequent follow-ups such as increased compliance to medications.

Limitations:

This study is limited in its design and scope from supporting any significant conclusions on the efficacy of the clinical approach presented. Although adverse events in three patients are unlikely to be due to the procedure performed, the absence of a control group prevents the elimination of this possibility. The results of this study suggest the need for a larger randomized trial.

Conclusions:

In this open labeled uncontrolled safety trial of helical needle TE delivery of autologous bone marrow, the lack of procedural complications, the statistically significant improvements in LV ejection fraction, and trend towards benefit in end-diastolic volume, 24 hour Holter, and exercise tolerance support the safety of this technology and suggest the need for a larger trial to determine the overall ability to improve LV dysfunction after myocardial infarction.