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INTRACORONARY TRANSPLANTATION OF AUTOLOGOUS HAEMATOPOIETIC STEM CELLS IN ISCHAEMIC END-STAGE LEFT VENTRICULAR FAILURE

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ABSTRACT

The prevalence of end-stage heart failure is rising despite presence of successful reperfusion strategies for treating acute myocardial infarction and advancements made in pharmacological and device therapy optimized for heart failure management. The non-availability of a mature cardiac transplantation programme and absence of left and right ventricular assist devices in many parts of the world has renewed interests in potential alternative options.

We demonstrate the preliminary observational data (not a trial) of a beneficial effect of intra coronary autologous bone marrow derived peripheral haemopoietic stem cell transplantation to improve myocardial contractility.

Systematic and cellular level analysis on these cells will be required to optimize therapeutic utility of this emerging regenerative medical speciality.

ABBREVIATIONS:

PCI -Percutaneous Coronary Intervention, CABG -Coronary Artery Bypass Grafting, TVD – triple vessel disease, LV EF -left ventricular ejection fraction, DHM -Dynamic Heart model, MR-Mitral Regurgitation, NSTEMI- Non-ST elevation myocardial infarction, STEMI- ST elevation myocardial infarction, LAD-Left anterior descending, NYHA – New York Heart Association

KEYWORDS: End-Stage Heart Failure, Intra-Coronary Transplantation, Autologous Bone-Marrow-Derived Peripheral Haematopoietic Stem Cells.

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1. INTRODUCTION

Worldwide, the prevalence of heart failure is estimated at 64.34 million cases (8.52 per 1,000 inhabitants), accounting for 9.91 million years lost due to disability [Lippi, 2020]. Deaths attributed to heart failure exceed the combined death toll for lung cancer, breast cancer, prostate cancer, and HIV/AIDS (Chen-Scarabelli, 2015) even in countries with developed medical facilities. Prognosis of the heart failure patients is poor, worse than that for many cancers (Kirkpatrick, et al 2007). Patients with NYHA class II symptoms are at a proportionally higher risk of sudden cardiac death while those with NYHA class IV symptoms have a one-year mortality as high as 75% with a significantly higher risk of dying of progressive heart failure characterized by worsening shortness of breath, orthopnea, hypotension, and decreasing level of consciousness. This illustrates the need for developing new therapeutic options in advanced heart failure.

Autologous bone marrow derived hematopoietic stem cells have been used for experimental or small-scale trials or registries in the context of heart failure or myocardial infarction since 2007 (Assmus et al, 2007 & Mills et al 2007) and more recently in dilated cardiomyopathies (Amoozgar H et al). Our group has previously reported one case of successful adaptation of intracoronary autologous transplantation of such cells in ischaemic end-stage heart failure, with subsequent ability to proceed for Rotablation assisted high risk PCI revascularization of the last remaining calcific coronary artery (Athauda arachchi et al, 2018). Multiple medical comorbidities, heterogeneous quality of cell harvesting, and delivery systems used, makes it difficult to systematically evaluate the benefit of this new therapy in end stage heart failure or long-term prognosis, as many organ dysfunctions have already set in at this stage.

We therefore evaluated our own collective experience of utilizing such stem cells, and we describe the safety aspects and immediate efficacy noted in left ventricular function, the detailed studies of which are ongoing.

2. METHODOLOGY

This was a simple observational study evaluating end stage heart failure patients with NYHA IV symptoms with LVEF <30% on maximal tolerable heart failure medications and unsuitable for device therapy or further revascularization.

Following haematological evaluation, patients were administered intravenous GCSF X 2-3 doses, with review of blood counts. Stem cells were harvested within set time periods using a haemocath dialysis catheter, placed in femoral vein, with the support of intravenous inotropes, and stem cells were harvested using Haemonetics MCS 971E kit. One (1 ml) stem cell harvest was sent for immediate sample analysis for CD34 count by nearest Flow cytometric facility on ice, and the remaining harvest (ranged from 25 ml to 35 ml, on average 30 ml), was delivered on ice for immediate intra coronary transplantation, after gentle warming. Cath lab procedure was undertaken within 15 minutes and intracoronary slow injection of stem cells was given using a microcatheter based injection system over 15 minutes. Pre and post echocardiographic assessment of LVEF was done using dynamic heart model (DHM), Simpson's biplane and strain pattern on Phillips Epic CVx echocardiographic platform.

The patients were observed after the index procedures, with their standard heart failure therapy being continued as appropriate, and the long-term outcome noted over a year.

3. RESULTS

Of a typical case, following GCSF, the total WBC count of the stem cell harvest was $303.4x10^3$ per microlitre and the CD34+ cell count was 3276 per microlitre. These CD34+ve cells constituted 24% of the CD45 negative cells (see Figure 1 annexed). This would suggest that approximately $9X10^9$ of CD34+ve haemopoietic stem cells should have been contained in total in the intracoronary injection (Figure 2).

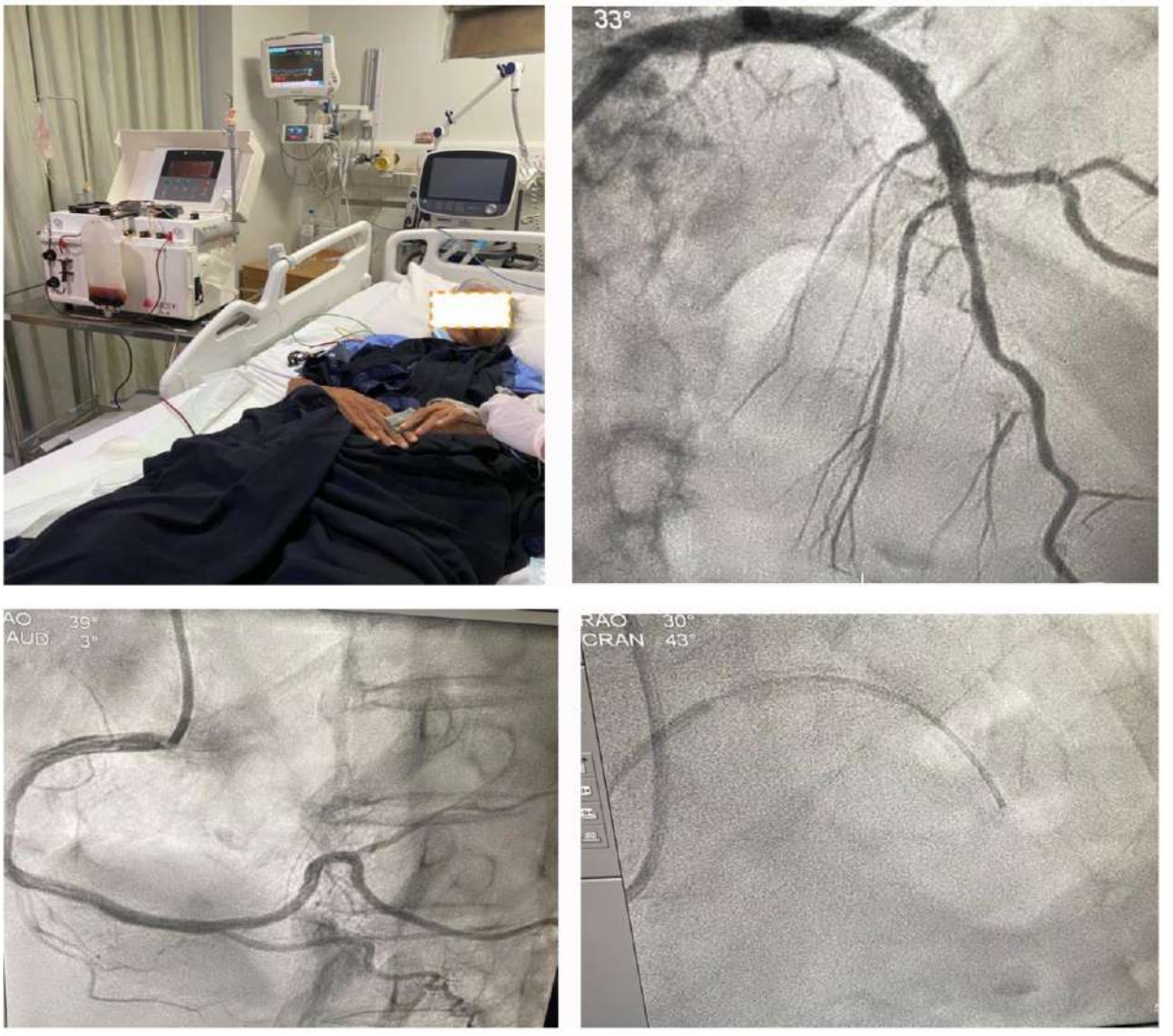

Figure 1: harvesting autologous haemopoietic stem cells in a coronary care unit , with monitoring facilities. Coronary angiogram: patent stent in previously infarcted LAD territory, recrossed with coronary microcatheter (standard interventional technique) to transplant the autologous stem cells

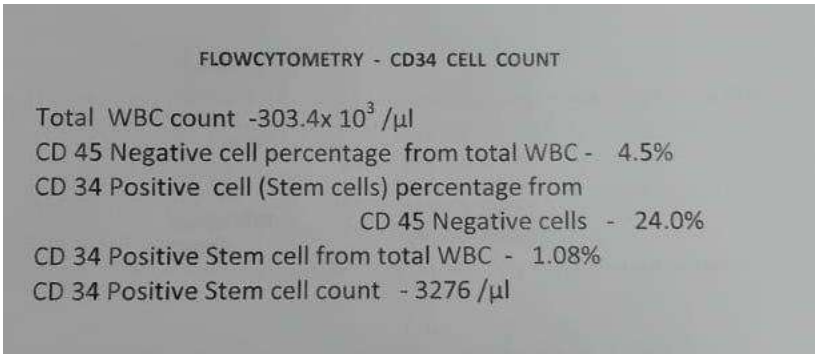

Figure 2: Flow cytometric analysis of cells derived using the Haemonetics kit, to calculate CD34+ve cell counts in the harvest

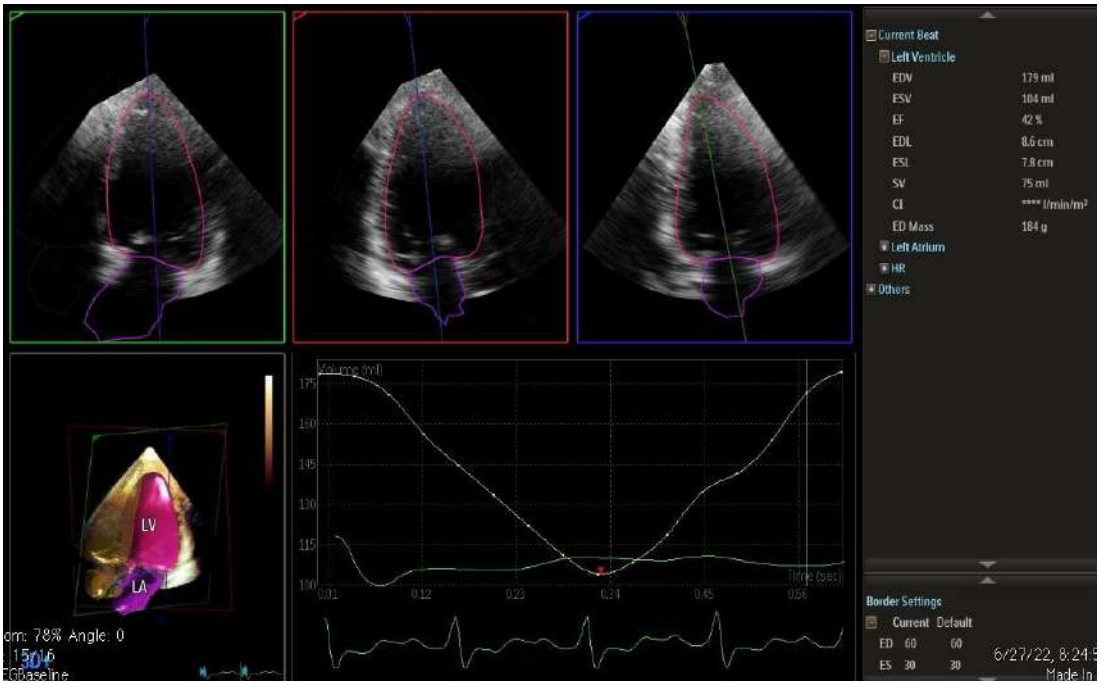

Figure 3: Intracoronary stem cell transplantation and Echocardiographic (DHM) LVEF assessment pre- and post-transplant (Illustrated above is the post-operative echocardiogram of subject 4).

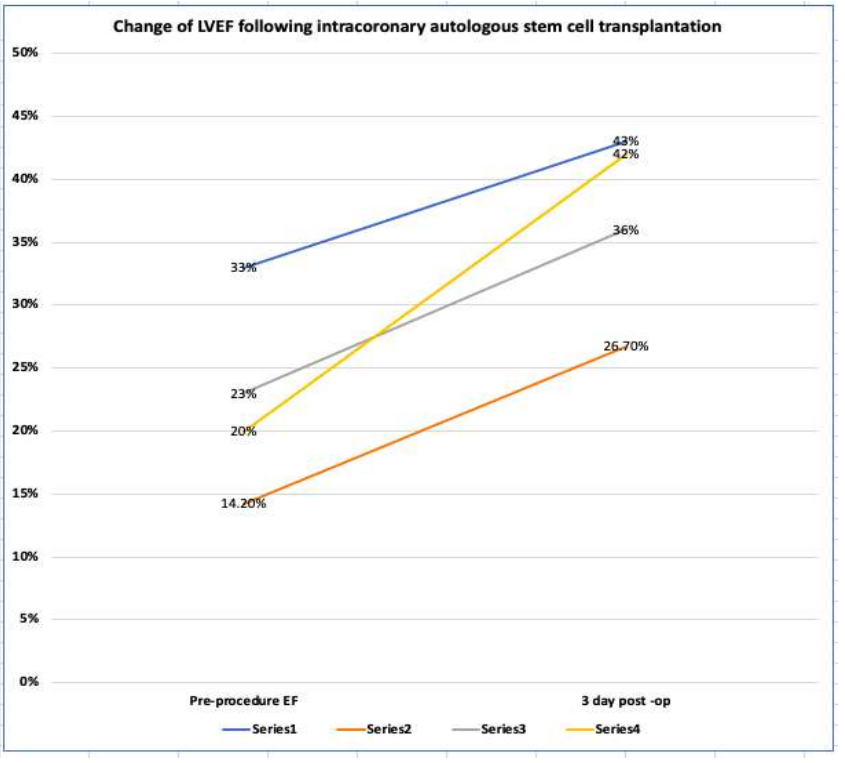

Figure 4: Observed early Change of LVEF following intracoronary autologous haematopoeitic stem cell transplantation (0 and 3 days)

The average age was 63.75 years and Preoperative LVEF was 22.55%+/-7.9%. Post procedure day 3, LVEF was 37%+/-7.5%, with an average increase of LVEF post procedure by 14%+/-5.25% (Figure 3).

In hospital major adverse cerebral or cardiac events (MACCE) was 0%, and all 4 patients reported improvement of their symptom of breathlessness corroborating with improvement of calculated LVEF noted within 72 hours of procedure in all the patients, with variable degrees (Figure 4).

On long term follow up of survival of these relatively ill patients, the eventual cause of death in 3 patients was deemed non-cardiac, and one patient is still alive being followed up in heart failure clinic (Figure 5). However, the study being an observational finding of cases and having a very limited number of end-stage heart failure patients, no inferences could be drawn on mortality from this data. However, in all the cases listed as above, no immediate or late cardiac or extra-cardiac complications were noted.

Patient details	Indication	Pre-op LVEF	Day3 post -op LVEF	Intra op or in-hospital complications	Long term outcome
Male, 74 years	CABG post MI, poor LVEF, narrow QRS, repeated and frequent hospitalization despite maximal tolerable medical therapy	33%	43%	No	Survived 1.5 years(non-cardiac death-?(CVA). Had only 1 heart failure hospitalization till time of death .
Female, 63 years	Severe calcific TVD, turned down for CABG, repeated NSTEMI, severe SOB and HF hospital admissions	14.2%	26.7%	No	Improved EF and less SOB, could then proceed to Rotablation assisted PCI to LAD (last remaining vessel), improving LVEF further to 36.1%. No recurrent hospitalizations. Survived 2 years (non-cardiac death? GI bleed)
Male, 38 years	Late(>4d) presenting Ant STEMI, severe TVD, complicated PCI to LAD and severe residual LVSD , with no response to maximum tolerated medical therapy>1 year and primary prevention AICD in place. Repeated hospital admissions with pulmonary oedema	23%	36%	No	Improved physical activity and return to previous occupation. No further emergency hospital admissions. Survived for 18 months before sudden death during Covid lockdown after a respiratory illness.
Female,80 years	Late(>4d)presenting Ant STEMI, Late PCI, severe residual LVSD with MR, with no response to maximum tolerated medical therapy>1 year, considered but not suitable for CRT and unable to offer surgery or Mitra clip, repeated hospitalizations with heart failure	20%	42%	No	Less SOB and able to perform ADL better. Follow up ongoing. Patient alive.

Figure 5: Summary table of characteristics and long term outcomes of 4 subjects with end-stage heart failure, undergone intracoronary stem cell transplantation once and followed up in clinic.

4. DISCUSSION

In our patients with end stage ischaemic cardiomyopathy, the intracoronary transplantation of autologous bone marrow derived haemopoietic stem cells harvested from peripheral blood resulted in the improvement of the symptoms of heart failure and left ventricular systolic function without significant immediate peri-procedural complications.

This was a consistent finding in all the patients studied irrespective of age or sex, albeit with a very small number of subjects. However, it is not clear how long the effects would last and whether repeated therapy would improve function further or if adverse events would increase in subsequent attempts. The mode and cellular mechanisms of the benefits noted above requires further analysis at cellular and molecular level.

5. CONCLUSION

The intracoronary transplantation of autologous, bone marrow derived haematopoietic stem cells, harvested from peripheral blood, offers another investigative therapeutic option for improving symptoms or echocardiographic features of end stage heart failure once all other therapeutic options have been tried maximally. This is important, as the supply of cadaveric heart transplants are in short supply. This new regenerative therapy should be assessed further for identifying ways to improve long term outcomes in end-stage heart failure.

6. ACKNOWLEDGEMENTS

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