MAR Cardiology & Heart Diseases (2023) 3:6

Research Article

Efficacy and Safety of Intracoronary Transplantation of Peripheral Blood-Derived Mononuclear (Pbmncs) Autologous Stem Cells in Patients with Acute Myocardial Infarction: A Prospective Pilot Study from North India (Itpasc Study)

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Received: 27 September 2023

Published: 16 October 2023

Abstract

Background: *Myocardial necrosis starts rapidly after coronary occlusion, usually before reperfusion can be achieved. Cardiac transfer of Bone marrow and human peripheral blood mononuclear cells (PBMNCs) -derived stem cells can have a favourable impact in patients with myocardial infarction.Our study using transplantation of non-expanded peripheral blood mononuclear cells(PBMNCs) improved the cardiac function in patients with Myocardial infarction and is safe and feasible. It is ist prospective pilot study from region with six months of follow-up. 10 Patients of ST-elevation acute anterior wall Myocardial infarction with occlusion of left anterior descending were taken for Echocardiography (2 blind operators) before coronary intervention. Percutanous coronary intervention of left anterior descending (LAD) by drug eluting stent followed by intracoronary infusion of PBMNCs was done. 10 patients of acute anterior wall myocardial infarction were taken as control in whom only LAD stenting was done. Echocardiography was carried out on follow up for assesment of functions.*

Results: *After Six months of follow up in both case and control group there was improvement in left ventricular functions. But Left ventricular functions improvement in cases where intracoronary stem cell therapy was given in addition to LAD stenting which was statistically significant (P-value <0.05) in stem cell therapy group.*

Conclusion*: Intracoronary PBMNCs infusion is a less invasive, more feasible, safer and a novel therapy for acute myocardial infarction patients who have depressed cardiac function.It causes significant improvement in Ejection fraction and wall motion score index which are most important prognostic factor in myocardial infarction patients.*

Keywords: *Stem cell, Echocardiography, STEMI*

Abbreviations

ACEI	Angiotensin converting Enzyme inhibitor
AAMI	Acute Anterior wall myocardial infarction
AMI	Acute myocardial infarction
MI	Myocardial Infarction
PCI	Percutaneous Coronary intervention
LAD	Left anterior Descending coronary artery
PBMNCs	Peripheral Blood Derived Mono Nuclear Stem Cells
BMCS	Bone marrow cells
BMMNCS	Bone marrow mononuclear cells
TLC	Total Leukocytes Count
Hb	Hemoglobin
LDL	Low- Density Lipoprotein
HDL	High Density Lipoprotein
TG	Triglycerides
ML	Milliliter
EDV	End Diastolic volume
ESV	End Systolic volume
SV	Stroke Volume
LV-EF	Left Ventricular ejection fraction
LV	Left ventricle
IVSed	Inter ventricular septal thickness end diastolic
IVSes	Inter ventricular septal thickness end systolic
WMSI	Wall motion score index
Cu.mm	Cubic millimeter

SD	Standard deviation
EPCS	Endothelial progenitor cells
C.I	Confidence interval
MNC	Mono Nuclear cells
MM	Millimeter
MRI	Magnetic resonance imaging

Introduction:

Background: Myocardial necrosis starts rapidly after coronary occlusion, usually before reperfusion can be achieved. The loss of viable myocardium initiates a process of adverse left-ventricular remodelling leading to heart failure. Cardiac transfer of Bone marrow and human peripheral blood mononuclear cells (PBMNCs) -derived stem cells can have a favourable impact in patients with myocardial infarction. With this background knowledge this study was planned to be carried out. Because the invasiveness of Bone marrow stem cell collection (BMC) in Myocardial infarction limits its clinical application, we hypothesized that transplantation of non-expanded peripheral blood mononuclear cells(PBMNCs) will be safe to perform and improve the parameters of left Ventricular functions in patients with Myocardial infarction.

Methods

AIM:1. Test the efficacy, safety and feasibility of intracoronary transplantation of non-expanded (PBMNCs) autologous stem cells in patients with acute myocardial infarction.

2. To examine the effect of intracoronary transplantation of non-expanded PBMNCs on Left ventricular(LV) Functions, as measured by LV ejection fraction (LVEF), after Myocardial infarction and as well as to assess the effect on regional wall Motion and cardiac volumes in these patients.

Study subjects: Patients of Acute Anterior wall (AAWMI) ST-elevation Myocardial infarction admitted in the Department of cardiology, of this Institute were included in the study. Informed consent was taken from all patients participating in the study. Patients were Non-Randomly allocated in a 1:1 ratio to either the control or non-expanded peripheral blood mononuclear cells (PBMNCs) group. All patients underwent 2D-Echocardiography before intervention and after six months of followup by 2 blinded operators. Patients in PBMNCs and Control group had proximal Left anterior descending (LAD) coronary artery occlusion on coronary artery angiography. Stenting of Proximal LAD of Both groups of patients was performed within hours of presentation. Patients of PBMNCs group were taken for stem cell harvest after Proximal LAD stenting and intracoronary infusion of stem cells was performed within 24-48 hours of Proximal LAD stenting in this group of patients. Whereas control group received only Stenting of the Proximal LAD within hours of presentation.

Inclusion criteria: Patients between 18 and 70 years of age with Acute Anterior wall (AAWMI) ST-Elevation Myocardial infarction were eligible for inclusion in the study.

Exclusion criteria:

(i) Cardiogenic shock

(ii) Pulmonary edema.

(iii) Advanced hepatic or renal dysfunction

(iv) Evidence of malignant diseases

(v) LVEF <20%

Methodology

Preparation of Progenitor Cells: A Stem cell separator apheresis system with computer software (COBE Spectra, software version 7.0) from Bio Cell was used to collect all PBMNC products via the standard Mono Nuclear Cell (MNC) program. Acid citrate dextrose-A (ACD-A) was used as the anticoagulant. Apheresis was performed through femoral vein in all patients in the PBMNC group.

Stem cell harvest solution obtained from patients by COBE Spectra-apherisis was concentrated to about 20 ml of final volume by Density Gradient Centrifugation. Mono Nuclear Cell (MNC) and CD34+ cell count of stem cell solution was performed. Mono nuclear cell count and CD34+ cell count of the stem cell harvest fluid was done by ISHAGE protocol with FACS Calibur (Becton Dickinson) Flow Cytometer Made in USA. MNC count was also done by using Automated Cell counter and manual DLC.

Catheterization Procedure for Progenitor Cell Transplantation: An over-the wire balloon catheter was advanced into the infarct-related artery. To allow for adhesion and transmigration of the infused cells through the endothelium, the balloon was inflated inside the stent previously deployed during acute reperfusion of infarct related artery with low pressure to block blood flow for 2 minutes while 5 ml of the PBMNCs suspension was infused distally to the occluding balloon through the central port of the balloon catheter. This manoeuvre was repeated 4 times to accommodate infusion of the total 20-ml of stem cell suspension, interrupted by 2 minutes of reflow by deflating the balloon. In control only proximal LAD stenting was performed.

PCI of proximal LAD of both cases and controls was performed by using drug eluting stent within 24 hours of presentation. Intracoronary transfer of stem cells was performed with in 24-48 hours of performing PCI of Proximal LAD in cases only.

2D-Echo Cardiography: For the assessment of Left ventricular (LV) functions and regional LV wall motion, 2D- Echocardiography (Phillips Epiq 7) was carried out before intracoronary Stem cell transplantation and coronary intervention in both case and control group and again at 6 months of follow-up by 2 operators who were blinded both times for cases & control groups. Two-dimensional resting echocardiography was performed in the 4 standard views (parasternal long-axis and short-axis views and apical 4- and 2-chamber views) and regional LV wall motion analysis was performed as described by the Committee on the Standards of the American Society of Echocardiography, dividing the left ventricle into 17 segments and scoring wall motion as 1=normal, 2=hypokinesis, 3=akinesis, 4=dyskinesis for each segment. The wall motion score index (WMSI) was calculated as the sum of the scores of the segments divided by the number of the segments evaluated was calculated prior to

intervention, at one and 6 months of follow up. Left ventricular systolic (ESV/ml) and diastolic volumes (EDV/ml) were calculated by Simpson's Rule. Stroke volume (SV/ml) and left ventricular ejection fraction (LVEF %) were calculated by Simpson's Rule. Inter ventricular septal wall thickness at end diastole (IVSed/mm) and at end systole (IVSes/mm) were measured.

Statistical Analysis: Data were explored for any outliers, errors and missing values. Quantitative data were described as mean and standard deviation. Frequency distribution of study characteristics were shown separately for patients with and without various outcomes. Comparison of various outcome groups was carried using Chi-square test of association (with Fisher's exact test if cell frequencies were small) to find out their statistical significance. Comparison of baseline and followup data was done using paired analysis with Wilcoxon Signed rank test. Univariate odds ratio and its 95% confidemce interval (C.I.) were also calculated to identify significant improvement of parameters of left ventricular functions. All statistical tests were two-tailed and p-value (two-tailed) <0.05 was taken as significant.

Results

This was a Prospective Non- Randomized case control clinical Pilot Study. Study was conducted over a period of 2 years. 10 patients of fresh acute anterior wall ST- elevation Myocardial infarction were taken as cases in whom PCI of Proximal LAD was performed within hours of presentation, followed by intracoronary infusion of Peripheral blood derived Mono nuclear stem cells (PBMNCs) within 24-48 hours of Performing PCI.10 patients of acute anterior wall ST elevation myocardial infarction with matching clinical profile with cases were taken as controls. Control group received only Stenting of the Proximal LAD within hours of presentation. Stem cell harvest was not performed in Controls.

Table 1: Clinical characteristics of study population

	Cases(n=10)	Control(n=10)	p value
Age, years	58.8 ± 7.5	59.7 ± 6.5	0.54
Male sex, no(%)	10 (100)	10 (100)	
Diabetes, no.(%)	2 (20)	2 (20)	
Dyslipidemia, no.(%)	10 (100)	10 (100)	
Smoking, no.(%)	10 (100)	10 (100)	
Killip class on admission			
I	6 (60%)	6 (60%)	
II	4 (40%)	4 (40%)	
Mean transplantedCD34+ cells, no	4.5 x 10^6 ± 0.44	-	
Mean transplanted cells, no	5.62 x 10^9 ± 0.6	-	
Revascularization time (hours)	7.8± 2.3	8.7 ± 2.0	0.51
Medication			
ACEI/ARB, no(%)	10 (100)	10 (100)	
Beta blockers, no.(%)	10 (100)	10 (100)	
Statins, no(%)	10 (100)	10 (100)	
Aspirin, no(%)	10 (100)	10 (100)	
Clopidogrel, no(%)	10 (100)	10 (100)	

Data expressed as Mean±SD; ACEI, Angiotensin-Converting Enzyme Inhibiter, ARB -Angiotensin receptor blocker

Table 2: Left ventricular functions of Stem cell therapy group at base line and at followup (2D-Echocardiography):

Variable	Mean±SD (Baseline)	Mean±SD (Followup)	Mean Difference	95%C.I, lower--upper	P-value
EDV(ml)	134±44.35	122.6±37.44	11.4	3.97---18.82	0.007
ESV(ml)	83.1±38.5	59±30.4	24.1	16.8—31.4	0.007
SV(ml)	51±14.8	62.1±19.9	-11.1	-16.4---5.8	0.001
LVEF (%)	40.79±9.11	53.68±11.7	-12.89	-15.86---9.91	0.001
WMSI	2.39±0.25	1.37±0.3	1.02	0.94---1.09	0.001
IVSed(mm)	10.1±1.1	11.7±1.1	-1.6	-2.1---1.09	0.001
IVSes(mm)	12.2±1	13.7±0.8	-1.5	-1.8---1.12	0.001

EDV, End Diastolic Volume; ESV, End Systolic Volume; SV, Stroke Volume; LV-EF, Left Ventricular Ejection fraction; WMSI, Wall Motion score Index; IVSed, Inter Ventricular Septal End Diastolic thickness; IVSes, Inter Ventricular Septal End Systolic Thickness

Intracoronary stem cell therapy group had significant improvement in various parameters of left ventricular systolic function at followup compared to baseline. Significant Improvement in wall motion abnormality was also observed. Patients of stem cell therapy group had no cardiac and noncardiac adverse events over a followup period of six months. Intra coronary Stem cell therapy was also found to be safe and feasible in patients of acute anterior wall ST-Elevation myocardial infarction having left ventricular systolic dysfunction at presentation.

Table 3: Left ventricular functions of Control group at baseline and at followup (2D-Echocardiography)

Variable	Mean±SD (Baseline)	Mean±SD (Followup)	Mean Difference	95%C.I, lower--upper	P-value
EDV(ml)	133.4±42.6	126.3±40	7.1	0.85---13.34	0.03
ESV(ml)	81.6±38	72.4±35	9.2	3.8---14.57	0.004
SV(ml)	52.07±12.6	53.9±13.2	-1.9	-3.65—2.27	0.61
EF (%)	40.7±9.5	44.8±10.4	-4.1	-5.5--- -2.55	0.001
WMSI	2.39±0.25	1.87±0.2	0.52	0.40—0.64	0.001
IVSed(mm)	9.9±0.88	10.5±1.2	-0.6	-0.96-- -0.23	0.005
IVSes(mm)	11.9±0.87	12.6±0.843	-0.7	-1.04-- -0.354	0.001

Table 4: Left ventricular functions and volumes of study population at baseline

Variable	Case Mean±SD	Control Mean±SD	Mean difference	95%C.I Lower--upper	P-value
EDV(ml)	134±44	133±42	0.6	-40.29—41.49	0.970
ESV(ml)	83±38	81±38	1.5	-34.41—37.41	0.880
SV(ml)	51±15	52±13	1.1	-11.88--14.02	0.820
EF (%)	40.7±9	41±9.5	0.06	-8.67---8.796	0.879
WMSI	2.4±0.25	2.39±0.25	0.01	-0.23----0.234	0.907
IVSed(mm)	10.1±1.1	9.9±0.87	0.2	-0.734—1.13	0.677
IVSes(mm)	12.2±0.91	12±0.87	0.3	-0.543---1.143	0.444

Table 5: Left Ventricular Functions of the study population at followup (2D- Echocardiography):

Variable	Case Mean±SD	Control Mean±SD	Mean difference	95%C.I Lower--upper	P-value
EDV(ml)	122.6±37.4	126±39.7	3.7	-32.58---39.98	0.650
ESV(ml)	59.0±30.4	72.4±35	13.4	-17.39---44.23	0.226
SV(ml)	62.1±20	53.9±13	8.2	-6.762--25.442	0.151
EF (%)	53.7±11.7	44.8±10.3	8.9	-1.536--19.296	**0.045**
WMSI	1.37±0.3	1.87±0.20	0.5	0.265---0.734	**0.002**
IVSed(mm)	11.7±1.1	10.5±1.2	1.2	0.146--2.253	0.015
IVSes(mm)	13.7±0.8	12.6±0.84	1.1	0.317--1.883	0.010

Although both the groups had increase in left ventricular ejection fraction but Significant increase of Left ventricular Ejection fraction (LV-EF %) was observed in the stem cell therapy group compared to control groups at base line (C.I= -1.536--19.296, p-value=0.045).

Discussion:

The study Involved Intracoronary Transplantation of Peripheral blood derived Mono Nuclear autologous stem cells (PBMNCs) in 10 patients of Acute anterior wall myocardial infarction (AAWMI) in whom Percutanous coronary intervention (PCI) of Proximal LAD with drug eluting stents was performed immediately after presentation. Clinical characteristics of study population were noted in cases as well as controls (Table1). Results were compared after six months of followup with 10 matched controls of acute anterior wall myocardial infarction in which only PCI of Proximal LAD with drug eluting stents was performed without intracoronary transplantation of PBMNCs (Table2&3). Left ventricular functions of both group of patients were assessed at baseline and again after six months of followup by using 2D-Echocardiography (Table 4 &5).

We were able to demonstrate the feasibility and safety in collecting and transplanting (Intra coronary Transplantation) the peripheral blood derived autologous Mononuclear stem cells (PBMNCs) by using

intracoronary route (Proximal LAD) in patients of acute anterior wall myocardial infarction who were having depressed left ventricular functions on dual antiplatelet therapy (Aspirin 150 mg/day and Clopidogrel 150mg/day). Previous studies had emphasized the feasibility and safety of bone marrow cell (BMCs) aspiration, this procedure is always associated with high risk of life threatening bleeding episodes from bone in patients receiving dual antiplatelet therapy.

Other important observation of the present study was that the intracoronary administration of non-expanded PBMNCs (Stem cells) significantly enhanced the recovery of Left Ventricular contractile functions in patients optimally treated for Acute Anterior Wall ST-Elevation Myocardial infarction (AAMI). After 6 months of followup, the absolute increase in LVEF (ΔEF) was significantly higher in the Stem cell therapy group (12.89%) compared to controls (4.1%). Absolute increase in LVEF was 8.9% greater in stem cell therapy group compared to absolute increase in LVEF in control group after six months of followup. The enhanced recovery of LV contractile function after the administration of PBMNCs (stem cell therapy) appeared to be related to a reduction in Wall Motion Score Index (WMSI) within the territory of the infarct, because Stem cell therapy resulted in a greater tendency of significant improvement of WMSI compared with controls. ΔWMSI improvement was significantly more in stem cell therapy group (ΔWMSI =1.02) as compared to controls (ΔWMSI =0.52) after six months of followup (Table2&3).

There are also a few other studies which have shown benefit of intracoronary infusion of PBMNCs for Acute myocardial infarction (AMI) [1,2,3,4,]. Most important study among them is the "Japan Trial for Therapeutic Angiogenesis by Cell Transplantation of Peripheral Blood-derived Mononuclear Cells for Acute Myocardial Infarction (TACT-PB-AMI)". The primary aim of the study was to examine whether intracoronary injection of non-expanded PBMNCs results in an improvement in LV function, as measured by LV ejection fraction (LVEF), after AMI and at six months of followup[1]. This study included 18 cases and 36 controls of acute anterior wall myocardial infarction. Our study used same type of COBE spectra stem cell separator machine but our Machine was software 7.0 version compared to software 6.1 version used in TACT-PB-AMI study. Neither stem cell harvest nor Sham injection was performed in control group. Additional objectives were to test the feasibility and safety of this treatment, as well as to assess the effectiveness on regional wall motion, cardiac Volumes, and arrhythmias. The primary endpoint was the global left ventricular ejection fraction (LVEF) change from baseline to 6 months' follow-up. The data showed that the absolute increase in LVEF was 7.4% in the control group

and 13.4% (p=0.037 vs control) in the PBMNC group (Table 4 & 5). Our study was also based on same principles as the above mentioned study. Methods of stem cell (PBMNCs) harvest and processing were similar. Procedure of Intracoronary infusion of stem cells was also similar to the study mentioned above.

Present study showed similar improvement of LV functions comparable to the TACT-PB-AMI the study[1]. Data from our study showed that the absolute increase in LVEF was 4.1% in the control group and 12.89% (p-value=0.045) in the stem cell (PBMNCs) therapy group. Data from TACT-PB-AMI study showed that the absolute increase in LVEF was 7.4% in the control group and 13.4% (p-value=0.037) in the PBMNCs group. Improvement in LV functions observed in our study was comparable to the improvement in LV functions observed in TACT-PB-AMI study. Main difference between our and TACT-PB-AMI is related to number of patients included in study. TACT-PB-AMI included 18 cases and 36 controls where as number of cases and controls were 10 patients in each group in our study.

Other study which used intracoronary transfer of PBMNCs was The MAGIC cell randomized clinical trial[(3)] which 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 patients with myocardial infarction[(3)]. This study randomized 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. 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 [(3-5)]. High rate of in-stent restenosis at culprit lesion in patients who received G-CSF was found at follow up.

MAGIC cell Trial and our study both showed significant improvement of left ventricular functions following intracoronary stem cell infusion. Our study had advantage of absence of G-CSF related cardiac and noncardiac events. In our study we were able to obtain the required stem cell/PBMNCs number without using G-CSF. Patients who received G-CSF administration showed a tendency of modest increase of binary restenosis (50% vs 30%, P < .05) and a greater late loss of minimal luminal diameter (P >0 .05) at 6 months of follow-up, compared to the control group. Present study and (MAGIC Cell) 1 studies showed similar improvement in left ventricular functions. This study had a

followup of 2 years compared to six months in our study.

MAGIC Cell-3-DES (drug eluting stent) Randomized [2], Controlled Trial studied the efficacy of intracoronary infusion of granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs) in patients with acute (AMI) versus old myocardial infarction (OMI). The AMI cell infusion group showed a significant additive improvement in left ventricular ejection fraction (LVEF) and remodelling compared with controls (change of LVEF: +5.1±9.1% versus -0.2±8.6%, $P<0.05$; change of end-systolic volume: -5.4±17.0 mL versus 6.5±21.9 mL, $P<0.05$) [2]. G-CSF–based cell therapy did not aggravate neo-intimal growth with DES implantation. This study also showed that G-CSF–based stem cell therapy with DES implantation is both feasible and safe, eliminating any potential for restenosis. Results of our study were similar to MAGIC Cell -3-DES study.

Other studies related to AMI used Bone marrow as a source of stem cell where as our study used peripheral blood as source of autologous stem cell for intracoronary infusion. The BOOST [6] study was the first randomized controlled study to report a significant improvement in global LV function recovery after six months, expressed as a 6% incremental increase in LV ejection fraction (LVEF) evaluated using magnetic resonance imaging (MRI) in patients who had received intracoronary cell infusion after a median of 4.8 days following index PCI [6].

The FINCELL[7] study is a multicenter randomized placebo-controlled trial including 80 patients with STEMI treated with thrombolysis followed by PCI and stenting 2–6 days after the acute coronary event [7]. Patients were randomly assigned to receive intracoronary mixed bone marrow cells or placebo solution infused into the infarct-related coronary artery immediately after stenting. This study confirmed that intracoronary administration of bone marrow cells is safe in STEMI patients treated with thrombolytic therapy followed by PCI and is associated with an incremental improvement of global LVEF.

There are few studies related to Bone Marrow derived intracoronary autologous stem cell therapy in AMI which have not shown significant improvement in Left Ventricular functions. The Polish REGENT trial [8] was a randomized but not placebo-controlled multicenter trial including 200 AMI patients with baseline LV-EF ≤40% undergoing primary PCI [8]. Patients were randomly assigned to selected CD34+CXCR4+ bone marrow cell infusion, unselected mononuclear cell infusion, or control (ratio 2:2:1). At six months, the increase in LVEF observed in the cell treatment groups was not

significantly different from the increase in control patients.

The HEBE trial is also a multicenter randomized but not placebo-controlled trial including 200 STEMI patients undergoing primary PCI [(9)]. Patients in eight medical centers in the Netherlands were randomized to intracoronary bone marrow–derived mononuclear cell infusion, mononuclear peripheral blood cell infusion, or primary PCI alone (ratio 1:1:1). Despite promising results in the pilot trial [(10-11)] , intracoronary infusion of bone marrow–derived cells failed to improve regional myocardial function recovery (primary endpoint) and global LV function and LV remodelling (secondary endpoints) in first-time large-STEMI patients undergoing PCI. Accumulating data point to reduced functionality of bone marrow cells in patients with severe and advanced ischemic heart disease [54] [(11)], and these recent observations may well have affected the outcome in REGENT and HEBE, which specifically targeted patients with large myocardial infarctions and more advanced atherosclerotic disease.

Several studies suggest that the level of circulating CD34+ EPCs is predictive of future cardiovascular events, and that bone marrow-derived CD34+ cells could be important for cardiovascular repair. In the present study, we used a mean of 5.6×10^9 PBMNCs containing ≈4.5×106 CD34+ cells for intracoronary injection and obtained an increase of 8.7% in ΔEF value. In the BOOST[6] and REPAIRAMI [(12)] trials, ≈2.5×109 unfractionated BMCs and ≈2.4×108 Ficoll-separated BMCs (≈2–3×106 CD34+ cells) were transplanted, with increases of 6% and 2.5% in ΔEF values, respectively. In contrast, in Janssens's [(13,14)] report and the ASTAMI trial, ≈3×108 Ficoll-separated BMCs (≈2.8×106 CD34+ cells) and ≈7×107 Ficoll-separated BMCs (≈0.7×106 CD34+ cells) respectively were used and there was no significant increase in ΔEF value. Importantly, our study results suggest that PBMNCs, which were even not culture-expanded, show great capability as a comparable cell source to BMCs.

In contrast to those previous studies using bone marrow as source of stem cell for intracoronary infusion, we could easily collect ≈5.6×10^9 cells PBMNCs, avoiding contamination with neutrophils, within 2-3 hours without any hemodynamic or bleeding problems. We could concentrate the collected PBMNCs to 20 ml by density gradient centrifugation aseptically through bag to bag, instead of by Ficoll gradient sedimentation methods used in previous studies using Bone marrow derived stem cells. Our study therefore, show that intracoronary Infusion of non-expanded PBMNCs alone can promote improvement of LV functions without any bleeding accident or G-CSF-related serious adverse effects. Because we can easily obtain levels of ≈4.5×10^6 CD34+ cells, which are higher than in either the

BOOST^{2} [6] or REPAIR-AMI [12] trials, we never need another laboratory to expand the PBMNCs, suggesting the potential of this protocol to be easily adopted in any hospital worldwide.

All the patients who received intracoronary stem cell therapy and PCI to LAD were monitored at the time of stem cell harvest from Apherisis machine, at the time of intracoronary infusion and after that over a period of six months, for any adverse event. Stem cell harvest was tolerated well by all the patients. There was no cardiac and noncardiac adverse event during stem cell harvest. All patients tolerated the procedure of intracoronary infusion of stem cells over the LAD stent by using over the wire (OTW) balloon catheter. There was no cardiac and noncardiac adverse event during the intracoronary infusion of stem cells and immediately after the procedure. Stem cell therapy was also found to be more feasible because it was tolerated by all the patients who had Left ventricular dysfunction and bleeding tendency as the method of the stem cell harvest was non invasive as compared to other Invasive methods of stem cell harvest. Over a period of six months of followup there were no cardiac/noncardiac adverse events attributable to intracoronary stem cell therapy.None of the patients in either group had evidence of heart failure at six months of followup. None of the patients in either group had repeat episode of fatal and non fatal myocardial infarction.

Conclusion:

This is the first Indian study for autologous stem cell transplant in acute myocardial infarction. Our study shows harvesting stem cells and intracoronary transplantation is safe, feasible and cost effective with encouraging long term results in heart function (LVEF). It can reduce the heart failure in long term post myocardial infarction and opens new window in management of STEMI. The study may need to be operated and elaborated in a large number study in our set of population where affordability always is an issue.

Limitation:A major limitation of our study is that evaluation of the present regeneration therapy was not randomized, double blind, and controlled. Although we choose contemporary controls, the control group does not reproduce the exact Conditions of the cell therapy group to which the cells were transferred, including PBMNCs collection and a placebo intracoronary injection. Therefore, the true

benefit of cell transfer cannot be fully appreciated and further research is needed to address these issues. Although the number of patients in our study was small, but considering the nature of this elaborate procedure it appears that however a larger study is needed to substantially confirm these findings. Intracoronary infusion of PBMNCs in patients with AMI is associated with improved global LV contractile functions. Intracoronary stem cell therapy preferentially improves LV functions in patients with relatively depressed contractility after AMI, prevents end-diastolic and end-systolic LV volume expansion, and has not increased any adverse clinical events so far. Transplantation of PBMNCs might be an effective and novel therapeutic option for AMI, if cell transfer occurs expeditiously and in appropriate subjects. This less invasive and more feasible approach to collecting Stem cells may be a novel therapeutic option for improving cardiac function after AMI. MRI was not done in view of cost effectiveness and in acute MI time consuming out of monitoring was difficult & not cleared by ethical committee.

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