Transcoronary Injection of Angiogenic Cells Precursors an Autologous Stem Cell in Ischemic Cardiomyopathy: A Clinical study of 106 cases in Thailand

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Abstract

Objective: To assess the safety and efficacy of transcoronary injection of angiogenic cells precursors (ACPs) in patients with ischemic cardiomyopathy.

Methods: Between 2005 and 2008, 106 ischemic heart disease patients on maximal medical therapy and no option for revascularization procedures who underwent transcoronary injection of angiogenic cells precursors at Chaophya hospital, Bangkok, Thailand were enrolled in the study.

Results: Baseline study: The mean age of 106 patients was 66 ± 10.6 years. Majority of patients had Canadian Cardiovascular Society (CCS) class and New York Heart Association (NYHA) functional class III- IV. Most patients had poor left ventricular systolic function. At 1 year follow-up, there was significant improvement of CCS class from 2.63 ± 0.66 to 1.53 ± 0.76 (N = 39, $p < 0.001$) while NYHA functional class improved from 2.69 ± 0.56 to 1.64 ± 0.83 (N = 32, $p < 0.001$). Post treatment at 2-4 months, patients with poor left ventricular ejection fraction (LVEF ≤ 40%) at baseline, the LVEF was increased from 34.4% ± 16.4% to 39.1% ± 15.5% (N = 39, $p < 0.05$). The quality of life by SF-36 version 2 Health Survey revealed that General Health and Physical functioning were significantly improved. Procedural mortality rate was 0%.

Conclusions: Transcoronary injection of angiogenic cells precursors improved cardiac function (increased LVEF), exercise capacity and quality of life with high safety profile for ischemic cardiomyopathy patients with no-option revascularization.

Keywords: Angiogenic cells precursors, Transcoronary injection, Ischemic cardiomyopathy

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Introduction

Coronary artery disease (CAD), one of the most common consequences of atherosclerosis is presently the most common cause of heart failure in the world. Conventional therapy for heart failure associated with coronary artery disease namely medical, surgical, transcatheter revascularization, cardiac resynchronization therapy, cardiac ablation and automatic implantable cardiac defibrillator etc. are being widely used to treat heart failure, fatal dysrhythmias and sudden death in patients with end-staged ischemic heart disease. Despite the availability of all these new therapeutic modalities, some 5-10 % of CAD patients who have diffuse coronary disease due to progression of atherosclerosis or inappropriate vascular trees not suitable for surgical or catheter revascularization continue to suffer from repeated angina pain with/or without heart failure. Recent studies had shed light of a new hope on stem cell therapy for these seemingly hopeless patients (no-option).

Several experimental studies in animals had demonstrated efficacy of the use of a variety of stem cells in restoring myocardial function and reducing infarct size in these infarct-induced animals (1-3). Theoretically and

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experimentally embryonic stem cells work most efficiently but its use in human is hampered by ethical, religious and political concerns. Recently adult stem cells from bone marrow (BM) or peripheral blood were found effective in vivo in improving cardiac function primarily via neovascularization which improves survival and function of viable myocytes (2-4).

The last six years had witnessed several clinical studies using BM mononuclear cells or Endothelial Progenitor cells (EPCs) in treating post myocardial infarction patients or chronic ischemic cardiomyopathy. Majority of these studies showed improvement of cardiac function with increased left ventricular ejection fraction, decrease left ventricular end-systolic volume, reduced infarct size, improved viability and improved exercise capacity in those cell-treated patients. Most impressively was the high safety profile of all these studies (4-6).

A recent meta-analysis of controlled clinical trials has confirmed the benefit of intracoronary cell therapy following percutaneous coronary intervention for Acute Myocardial Infarction (AMI) on cardiac function and remodeling (7).

Following a successful clinical trial in Thailand using blood-borne angiogenic cell precursors (ACPs) harvested from patient's peripheral blood, cultured and expanded in an appropriate medium injected intracoronarily in patients with no-optioned ischemic cardiomyopathy (8-9), we have consecutively treated a total of 106 patients who were considered in advanced-stage ischemic heart disease with no revascularization options and reported the result herein. The objectives of this study were to determine the safety and efficacy of intracoronary injection of ACPs in relieving symptoms of angina pectoris and congestive heart failure in chronic ischemic heart disease patients with maximal medical therapy and no option for revascularization procedures.

Methods

Between March 2005 and April 2008, 106 patients with chronic ischemic heart disease underwent transcoronary injection of ACPs, an Autologous Stem Cells. The study was approved by the Ethics Human and Research Committee of Chao Phya hospital. Informed consents were obtained from all patients before the procedure. This clinical study was a non-randomized, open-study of consecutive patients with severe chronic coronary artery disease on maximal drug therapy and no option for revascularization procedures.

Severe ischemic-heart patients who continued to have angina pain or heart failure symptom and not responsive to standard treatment (full medication, balloon angioplasty, coronary artery bypass grafting) were enrolled to receive transcoronary stem cell therapy. Patients were excluded for severe contagious disease e.g. HIV, hepatitis and also malignancy. The following laboratory tests were done: blood chemistry for fasting blood sugar, blood urea nitrogen, creatinine, electrolyte, liver function test, Troponin-T, creatine kinase MB isoenzyme , N-terminal brain-type natriuretic peptide, complete blood count before,12 and 24 hours after the procedure. Assessment of cardiac performance, area of ischemia and viability test were carried out at rest and with Dobutamine stress echo-cardiogram, nuclear cardiac imaging 99mTechnicium-methoxyisobutylisonitrile (99mTc-MIBI), 6-minute walk test, and treadmill exercise if feasible.

The adult stem cells used in this study were ACPs which were developed by VesCell technology (VesCell, TheraVitae Co. Ltd.) in Israel (9). The ACPs were derived from the patient's own peripheral blood of 250 ml. collected from the patients using the same techniques for general blood donation and delivered to the laboratory in Israel for cell culture and expansion. VesCell, a blood-derived autologous cell therapy product consisting of ex vivo enriched angiogenic cell precursors (ACPs) was developed by TheraVitae. A non-mobilized, blood-derived cell population consisting of low density cells, termed synergetic cell population (SCP), was isolated and cultured in the presence of serum-free medium (X-Vivo 15, Lonza, Walkersville, MD, USA) supplemented with growth factors and autologous serum to yield VesCell. Significant cell numbers ($>50\times10^6$) of ACPs exhibiting morphological, immunocytochemical and functional characteristics of the angiogenic cell lineage were obtained from blood samples. The ACPs expressed the hematopoietic stem cell (HSC) markers CD34, CD 133 and CD117, as well as specific angiogenic markers such as vascular endothelial growth factor receptors 2 (VEGFR2) also known as kinase domain region [KDR], CD144, and CD31; demonstrated

acetylated low density lipoprotein (AcLDL) labeled with 3,3 - dioctadecylo - xacarbocyanine perchlorate - uptake; formed tube-like structures in vitro; and secreted cytokines such as IL-8, VEGF and angiogenin (Ang) (9).The efficacy of the ACPs has recently been reported to restore cardiac function in the infarcted rat by either intracoronary or intramyocardial routes (10). The process of cell expansion from blood took 5 days. Following the completion of the cell manufacturing process, syringes containing the product are inserted in pouches and then placed in an insulated shipping system (which includes a mobile temperature recording device for shipment) for shipment to the Chaophya hospital. Cells are preserved in a cooling environment of 2-8 degree celsius with the temperature being recorded every 5 minutes. This shipping system was designed for keeping a temperature of 2-8 degree celsius for 24 hours.

Procedure

Under light sedation, fasting state and aseptic technique, patients underwent a routine coronary angiography using a percutaneous transfemoral approach. After coronary angiogram was done, a small balloon catheter was advanced over the wire into coronary arteries, their branches and/or venous or artery bypass grafts supplying corresponding areas of ischemia and hibernating myocardium. Balloon inflations were deployed to temporarily occlude the coronary flow and injections of ACPs were made into target vessels. Hemostasis at the groin was achieved following removal of the catheter. Patients were observed overnight in coronary care unit.

Clinical follow-up

Follow-up of patients were made mostly by patients' own cardiologists at 2, 4, 6 and 12 months according to the protocol because majority of patients were from abroad.

Outcome measurement

Results of transcoronary injection of angiogenic cells precursors (ACPs) in a consecutive series of 106 patients with ischemic cardiomyopathy were assessed by Canadian Cardiovascular Society (CCS) Angina Class Scales, New York Heart Association (NYHA) Functional Classification, Echocardiography, SPECT/Mibi and Quality of life by SF-36 short form. Complications and adverse events were recorded during and within 24 hours after the procedure. These parameters were obtained at the time of the baseline pre-procedure and repeated post-procedure at 2-4 months, 6-8 months, and 8-12 months of follow-up, respectively.

Statistical Analysis

The data were analyzed by using the statistical package for social science of the Windows program. Descriptive statistics including frequency, percentage, mean and standard deviation were used to analyze the data of patients. Statistical comparisons between initial and follow-up data were performed using a paired t-test.

Results

One hundred and six patients with ischemic cardiomyopathy underwent transcoronary injection of angiogenic cells precursors between March 2005 and April 2008.

Demographic characteristics of patients were depicted in Table 1. A total of 106 patients with ischemic cardiomyopathy were entered in the study. Overall, the mean age of these patients was 66 ± 10.6 years and the oldest was 95 years old; 91.5% were male, 8.5% were females and most patients (84.9%) were Caucasians. The majority of the patients (86.8%) had dyslipidemia. 47.2% had diabetes mellitus and 70.8% had severe left ventricular dysfunction with LVEF ≤ 40%, triple vessel disease (73.6%), percutaneous coronary intervention (75.5%), coronary artery bypass grafting(65.1%), prior myocardial infarction (61.3%), and history of congestive heart failure (83%). The means of number of ACPs (CD31+, CD34+) was 23.2 ± 14.6 million cells and viability was 96.7 ± 3.30%.

Majority of the patients had Canadian Cardiovascular Society (CCS) and New York Heart Association (NYHA) class III-IV (74.63% and 74.36%). Most patients had poor left ventricular systolic function, EF ≤ 40% by echocardiography and EF ≤ 40% by SPECT/Mibi, (70.8% and 64.21%) (Table 2).

Outcome of transcoronary injection of angiogenic cells precursors (ACPs) in a series of patients with ischemic cardiomyopathy

Table 3 showed summary of clinical result. Mean baseline Canadian Cardiovascular Society (CCS) score of 67 patients was 2.71 ± 0.65. The CCS score was improved at follow-up, showing a decrease from 2.71 ± 0.65 to 1.52 ± 0.76. When the comparison between CCS score

Table 1. Clinical characteristics (N = 106)

Baseline characteristics of the patients	Frequency (Percentage) or Mean (SD)
Age (year)	66 ± 10.6 (Min = 33, Max = 95)
Male : Female	97 (91.5) : 9 (8.5)
Clinical history	
Dyslipidemia	92 (86.8)
Diabetes mellitus	50 (47.2)
Hypertension	30 (28.3)
Chronic kidney disease	17 (16)
Sleep disorder/Depression	25 (23.6)
Smoking (current or former)	35 (33)
History of myocardial infarction	65 (61.3)
History of congestive heart failure	88 (83)
Left ventricular systolic function	
LVEF ≤ 40%	75 (70.8)
LVEF > 40%	31 (29.2)
Coronary artery disease	
SVD	15 (14.2)
DVD	13 (12.3)
TVD	78 (73.6)
History of PCI	
1-2 times	60 (56.6)
> 2 times	20 (18.9)
History of CABG	
1 time	58 (54.7)
2 time	11 (10.4)
Pacemaker and/or AICD	57 (54)
No. of angiogenic cells precursors x 106 cells:	
CD31+, CD34± mean (SD)	23.2 ± 14.6 (Min = 1.78, Max = 72.29)
Viability (%) – mean (SD)	96.7 ± 3.30 (Min = 81.5, Max = 100)

SVD = Single vessel disease; DVD = Double vessel disease; TVD = Tripple vessel disease; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass grafting; AICD = Automatic implantable cardiovertor-Defibrillator

result at baseline and follow up were performed with a paired t-test, the clinical condition of patients showed significant improvement ($p < 0.001$) - Figure 1A.

Patients with baseline NYHA score for whom follow up data were available at post treatment 2-4 months (63 patients), at post treatment 6-8 months (45 patients), and at post treatment 8-12 months (32 patients) showed improvement, mean NYHA from 2.78 ± 0.65 to 1.64 ± 0.83 When the comparison between NYHA score result at baseline and follow up were performed with a paired t-test, the result showed statistically significant improvement ($p < 0.001$) - Figure 1B.

In those patients with poor left ventricular function (EF ≤ 40%) at baseline, the LVEF was improved from

Table 2. Functional class and LV ejection fraction

Baseline Functional class and LVEF	Frequency (Percentage)
CCS (N = 67)	
Class I-II	17 (25.37)
Class III-IV	50 (74.63)
Mean = 2.71 ± 0.65 (Min = 1, Max = 4)	
NYHA (N = 80)	
Class I-II	20 (26.32)
Class III-IV	58 (74.36)
Mean = 2.78 ± 0.65 (Min = 1, Max = 4)	
Ejection fraction by echocardiography (N = 106)	
≤ 40%	75 (70.8)
> 40%	31 (29.2)
Mean = 35.99 ± 15.84 (Min = 13, Max = 79)	
Rest EF by SPECT/Mibi (N = 95)	
≤ 40%	61 (64.21)
> 40%	34 (35.79)
Mean = 36.539 ± 15.90 (Min = 13, Max = 86)	

SVD = Single vessel disease; DVD = Double vessel disease; TVD = Tripple vessel disease; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass grafting; AICD = Automatic implantable cardiovertor-Defibrillator

35.99 ± 15.84 to 39.05 ± 15.51(3.06 points %) at 2-4 months, and to 37.04 ± 13.02 (1.05 points %) at 8-12 months. LVEF by SPECT/Mibi was improved from 36.53 ± 15.90 to 41.4 ± 15.1(4.87 points %) during the follow-up at 2-4 months. When the comparison between EF by echocardiography at baseline and follow-up were performed with a paired t-test, it showed significant improvement ($p < 0.05$, $p = 0.05$) however EF by SPECT/Mibi did not show statistically significant difference ($p > 0.05$)-Figure 2.

Figure 3 showed the result of SF-36 Version 2 Health survey in the present series. The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8 scale profile of scores as well as physical and mental health summary measures which range from 0 to 100, with higher scores indicating better health status. The outcome revealed that Physical Component Summary (PCS) was significantly improved in quality of life (QoL) in patients with post stem cells therapy 3-6 months but change in Mental Component Summary (MCS) was not significant because mental health was probably not a significant problem in majority of these patients before stem cell treatment (Table 4).

In our study, there was no serious adverse cardiac event such as death, myocardial infarction and/or ventricular tachycardia, during and after the administration of cell therapy. The procedure-related adverse events during hospitalization included mild heart failure (3 patients) that improved promptly with sublingual nitroglycerine and intravenous furosemide treatment, cerebral embolism (1 patient) which resolved in 12 hours, renal failure in 1 patient with advanced kidney disease requiring hemodialysis, hematoma at puncture site (1 patient), pneumonia (1 patient) and priaprism (1 patient).

Because majority of patients in the present series were in advanced stage of ischemic heart disease with additional several co-morbidities, the adverse events in the intermediate to long term follow-up for post-cell treatment were not unexpected and included myocardial infarction, hospitalization for heart failure, renal failure,

Table 3. Clinical results summary

Clinical results	Baseline	Post treatment 2-4 months	Post treatment 6-8 months	Post treatment 8-12 months
CCS	N=67	N=63	N=54	N=39
Mean (SD)	2.71±0.65	1.87±0.76	1.69±0.82	1.52±0.76
Comparison (baseline & post)				
Mean (SD)		2.73±0.63, 1.87±0.76	2.73±0.61, 1.69±0.82	2.63±0.66, 1.53±0.76
P value		p<0.001	p<0.001	p<0.001
NYHA	N=80	N=63	N=45	N=32
Mean (SD)	2.78±0.65	1.99±0.75	1.76±0.80	1.64±0.83
Comparison (baseline & post)				
Mean (SD)		2.76±0.67, 1.99±0.75	2.73±0.61, 1.76±0.80	2.69±0.56, 1.64±0.83
P value		p<0.001	p<0.001	p<0.001
Rest EF by ECHO: %	N=106	N=39	N=28	N=23
Mean (SD)	35.99±15.84	39.05±15.51	34.22±12.08	37.04±13.02
Comparison (baseline & post)				
Mean (SD)		34.4±16.4, 39.1±15.5	32.1±13.5, 34.2±12.1	32.5±10.4, 37±13
P value		p<0.05	p<0.05	p=0.05
Rest EF by SPECT: %	N=95	N=21	N=14	N=7
Mean (SD)	36.53±15.90	41.4±15.1	45.92±11.5	39.5±14
Comparison (baseline & post)				
Mean (SD)		40.8±17.3, 41.4±15.1	39.57±15.5, 45.92±11.5	45±9.9, 39.5±14
P value		p>0.05	p>0.05	p>0.05

and pneumonia as depicted in Table 5. At post-treatment 2-4 months follow-up, one of 98 patients (1.02%) -died due to pneumonia and sepsis. At post-treatment 6-8 months follow-up, three of 78 patients (3.85%) died; 1 sudden death probably due to recurrent MI, 1 kidney failure and 1 committed suicide. At post treatment 8-12 months follow-up, three of 51 patients (5.88%) died; 1 severe CHF with respiratory failure, 1 aortic aneurysm and pancreatic cancer, and 1 ventricular tachycardia with MI. Interestingly, four diabetic patients reported improvement in their diabetic status and glycemic control. One patient could stop insulin injection and switched to oral hypoglycemic agents. Three patients reported reduction of the dosage of oral hypoglycemic agents.

Figure 1. Comparison parameters before and after stem cell therapy of CCS and NYHA
A.CCS
B. NYHA

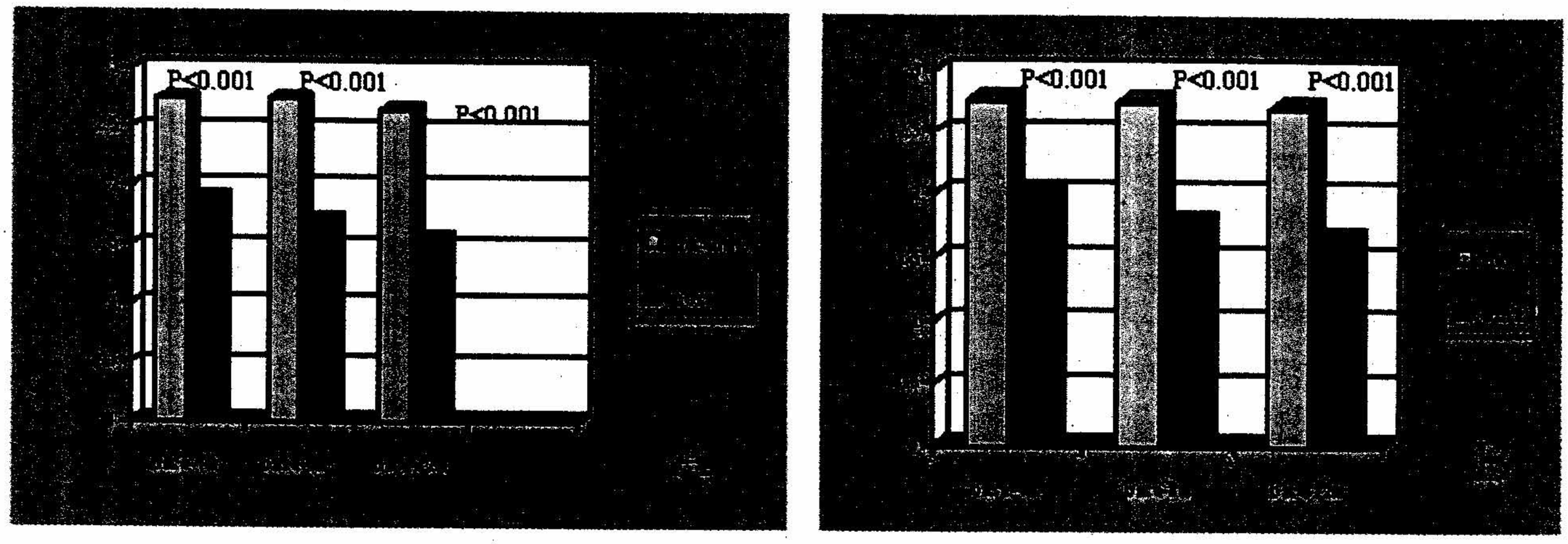


Figure 2. Mean of left ventricular ejection fraction (EF) by echo and by SPECT at baseline to post treatment 8-12 months follow-up

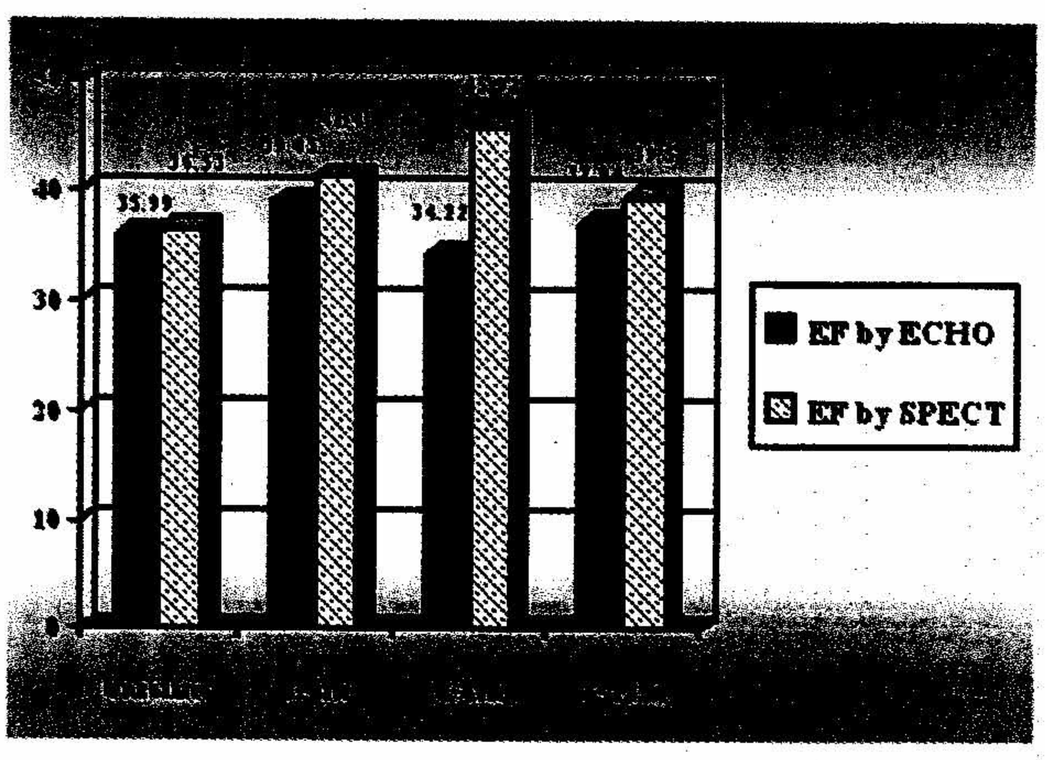
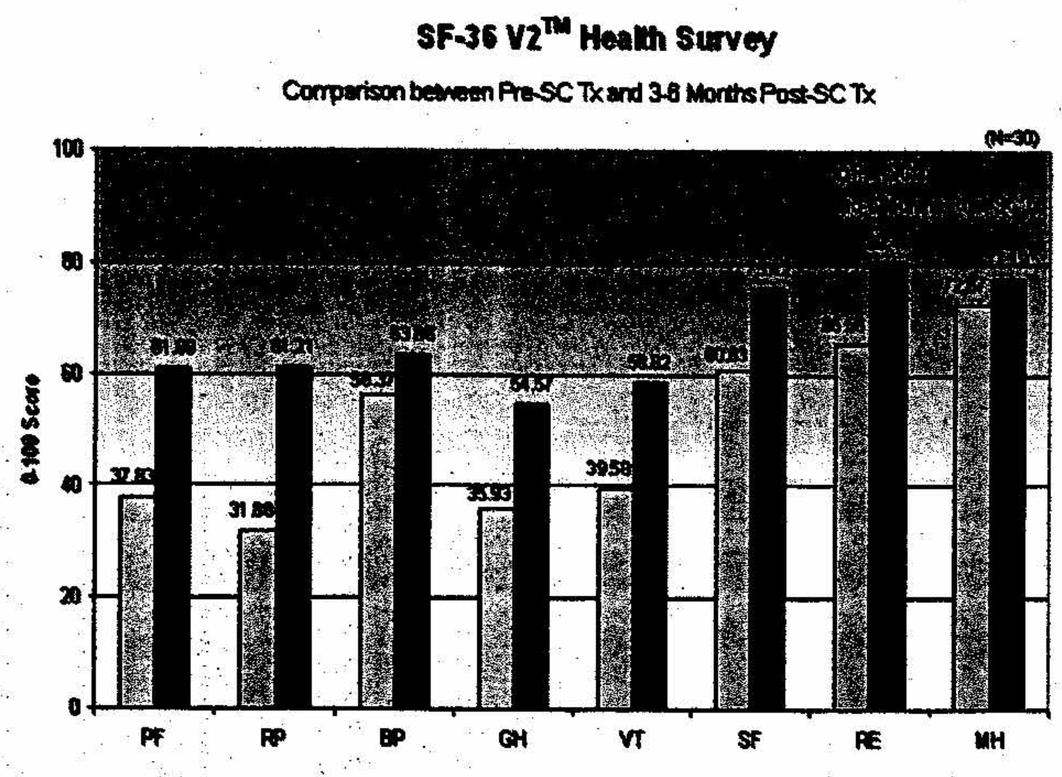


Figure 3. Comparison of quality of life by SF-36 version 2 between pre and post treatment stem cell



Discussion

The present study was aimed to examine the efficacy and safety of transcoronary transplantation of ACPs in patients with ischemic cardiomyopathy who had no therapeutic options e.g. CABG or PCI. The study has shown a high safety profile despite high-risk-category status in nearly two-third of the patients. There was no mortality related to the procedure or post-procedural hospital course. Majority of patients had previously undergone conventional intensive medical treatment, multiple percutaneous coronary intervention, surgical revascularization and device treatments and were having incapacitated symptoms and deteriorating clinical condition. Most patients had Canadian Cardiovascular Society (CCS) class and New York Heart Association (NYHA) functional class III- IV (74.63% and 74.36%) and also poor left ventricular systolic function, LVEF ≤ 40% by echocardiography and LVEF ≤ 40% by SPECT/ Mibi, (70.8% and 64.21%).

During the follow-up period, there were significant improvement of both CCS and NYHA. The CCS score showed a decrease from 2.63 ± 0.66 to 1.53±0.76 ($p < 0.001$) while NYHA functional class showed a decrease from 2.69 ± 0.56 to 1.64±0.83 ($p < 0.001$) at post treatment 8-12 months. Moreover in those patients who had poor left ventricular function (EF ≤ 40%) at

Table 4. Scores on the SF-36 version 2 health survey from baseline to 3-6 months (N = 30)

Domain	Pre-treatment	Post-treatment (3-6 months)	P value
0-100 Scores			
- Physical Functioning (PF)	37.83 ± 23.11	60.09 ± 25.12	<0.001
- Role-Physical (RP)	31.89 ± 23.17	61.21 ± 31.27	<0.001
- Bodily Pain (BP)	56.90 ± 27.56	63.86 ± 29.58	0.181
- General Health (GH)	34.79 ± 18.84	54.57 ± 25.26	<0.001
- Vitality	39.58 ± 18.95	58.82 ± 21.95	0.001
- Social Functional (SF)	60.83 ± 24.29	75.42 ± 24.67	0.014
- Role-Emotional (RE)	66.67 ± 32.35	80.46 ± 24.22	0.066
- Mental Health (MH)	72.67 ± 20.83	77.19 ± 17.36	0.233
Physical Component Summary (PCS)	30.75 ± 8.71	40.21 ± 10.71	<0.001
Mental Component Summary (MCS)	48.85 ± 12.39	51.37 ± 9.67	0.344

Table 5. Complication and adverse events during hospitalization and follow-up periods

Complication/ adverse events	In hospital (N = 106)	Post treatment 2-4 m (N = 98)	Post treatment 6-8 m (N = 78)	Post treatment 8-12 m (N = 51)
Event-no. (%)				
- Myocardial infarction	0	0	1(1.28%)	1*(1.96%)
- Hospitalization heart failure	3(2.83%)	2(2.04%)	1(1.28%)	1(1.96%)
- Cerebral embolism	1(0.94%)	1(1.02%)	0	0
- Ventricular tachycardia	0	0	0	0
- Renal failure	1(0.94%)	1(1.02%)	0	0
- Hematoma at puncture site	1(0.94%)	0	0	0
- Priaprism	1(0.94%)	0	0	0
- Pneumonia	1(0.94%)	1*(1.02%)	1(1.28%)	0
- Pancreatic cancer	0	0	0	1(1.96%)
- Death	0 (Death due to pneumonia)	1*(1.02%) (Death due to 1 myocardial infarction, 1 kidney failure, 1 suicide)	3(3.85) (Death due to 1 congestive heart failure, 1 aneurysm & pancreatic cancer, 1 ventricular tachycardia & myocardial infarction)	3*(5.88%)

*single patient

baseline, the Echocardiographic LVEF improved from 34.4 ± 16.4 to 39.1±15.5 ($p < 0.05$) at post treatment 2-4 months and also EF by SPECT/Mibi which improved from 36.53 ± 15.90 to 39.50 ± 14.0 during the follow-up to 12 months although it did not reach statistically significant difference ($p > 0.05$).

Our results are comparably similar to the other studies (11-13). Arom, et al (11). (2008) studied the efficacy of intramyocardial injection of angiogenic cell precursors for ischemic cardiomyopathy which showed that all patients tolerated cardiac surgery very well in the cell injection group. NYHA functional class improved from preoperative of 2.9 ± 0.7 to postoperative of 2.0 ± 0.9 ($N = 25$, $p < 0.001$). The LVEF improved by 6.4 ± 9.9 points % ($N = 25$, $p = 0.003$).

In our study, there were few adverse events such as local complication at puncture site (1 case), mild CHF, transient stroke (1 case), and renal failure (1 case) similar to complications from coronary angiogram procedure. There were seven deaths (6.60%) at follow-up period (12 months) which were not procedure-related but caused by sepsis, recurrent MI, kidney failure, CHF with respiratory failure, ruptured aneurysm and pancreatic cancer.

The present study demonstrated that the transcoronary injection of ACPs in patients with ischemic cardiomyopathy was feasible, safe and efficacious. EPCs have shown benefits in cardiovascular repair. EPCs naturally home to and engraft in the target site in response to stress signals in ischemic tissues (14-15). EPCs secrete a wide variety of chemo-attractants and trophic factors, resulting in the recruitment of additional cellular elements, tissue rescue and regeneration (16-17). ACPs are a subpopulation of EPCs which had recently been shown to restore function in the infarcted rat heart by promoting angiogenesis (10). Previous study had shown that human EPCs are capable to transdifferentiate in vivo into functionally active cardiomyocytes in mice (18). Whether ACPs helps regenerate new cardiomyocytes or promote mitosis of the existing cardiomyocytes in human remain enigmatic at present time. Future researches are needed to clarify this mechanism. Autologous cellular activity can be regulated by the body's natural mechanisms. Thus, stem/progenitor cell therapy has the potential to facilitate a safer and more efficient natural treatment. Finally, the use of peripheral blood as the "raw material" is much simpler and safer, as blood collection does not require any invasive procedures, anesthesia, or stem/progenitor cell mobilizing factors such as G-CSF, which may be harmful to cardiac patients (19).

Conclusion

Transcoronary injection of angiogenic cells precursors (ACPs) in no-option ischemic cardiomyopathy appears to be an effective therapy with high safety profile. The results of this study, which included 106 patients, indicated that this treatment is feasible, safe and efficacious to improve clinical condition such as angina and heart failure as well as LV function in chronic ischemic cardiomyopathy. No serious adverse effects were observed that could directly be related to the procedure and/or administered cells and beneficial effects were observed in a diverse clinical parameters, i.e. increased LVEF, improved NYHA functional class and CCS angina class as well as quality of life.

Limitations

Several limitations of this study need to be mentioned. This study is a report of case series without control cohort. Due to wide variation in clinical characteristics, various staging of the disease and diverse severity of patients' functional class, it was considered unethical to conduct a randomized control study in the present studied population. Statistical comparisons between initial and follow-up data that were performed using a paired t-test may affect validity and is prone to limitations inherent in such investigations, including the collection of non-randomized data, missing or incomplete information as these patients were mostly from oversea. Nonetheless, we believe that our data provide a real-world insight into the use of an autologous stem cell in patients with chronic ischemic cardiomyopathy.

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