Long-term effects of stem cell transplantation in heart failure

Dolgoročni učinki presaditve matičnih celic pri bolnikih s srčnim popuščanjem

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matične celice, dilativna kardiomiopatija, srčno popuščanje

Key words:
stem cells, dilated cardiomyopathy, heart failure

Abstract

Background: We investigated long-term effects of intracoronary transplantation of CD34+ cells in patients with dilated cardiomyopathy (DCM).

Methods: Of 110 DCM patients, 55 were randomized to CD34+ cell transplantation (SC) group, and 55 patients received no cell therapy (controls). In the SC group, peripheral CD34+cells were mobilized by G-CSF and collected via apheresis. Patients underwent myocardial scintigraphy and CD34+ cells were injected in the artery supplying the segments with reduced viability. Patients were followed for 5 years.

Results: At baseline, the 2 groups did not differ in age, gender, left ventricular ejection fraction (LVEF), or NT-proBNP levels. At 5 years, stem cell therapy was associated with an increase in LVEF (from 24.3 ± 6.5 % to 30.0 ± 5.1 %; P = 0.02), an increase in 6-minute walk distance (from 344 ± 90 m to 477 ± 130 m; P < 0.001), and a decrease in NT-proBNP (from 2322 ± 1234 pg/mL to 1011 ± 893 pg/mL; P < 0.01). During follow-up, 27 (25 %) patients died and 9 (8 %) underwent heart transplantation. Of the 27 deaths, 13 were attributed to pump failure, and 14 to sudden cardiac death. Total mortality was lower in SC group (8/55 [14 %]) than in controls (19/55 [35 %]) (P = 0.01). The same was true of pump failure (3/55 [5 %] vs. 10/55 [18 %], P = 0.03), but not of sudden cardiac death (5/55 [9 %] vs. 9/55 [16 %], P = 0.39). SC therapy was an independent predictor of outcome on multivariable analysis (P = 0.04).

Conclusions: Intracoronary stem cell transplantation may be associated with improved ventricular remodeling, exercise tolerance, and long-term survival in patients with DCM.

Izvleček

Namen: Z raziskavo smo želeli preučiti dolgoročne učinke intrakoronarne presaditve matičnih celic CD34+ pri bolnikih z neishemično dilatataivno kardiomiopatijo (DCM).

Metode: V prospektivno raziskavo smo vključili 110 bolnikov z DCM; od tega jih je 55 prejelo presaditev matičnih celic CD34+ (skupina SC), pri 55 bolnikih pa presaditve matičnih celic nismo opravili (kontrolna skupina). Pri bolnikih v skupini SC smo matične celice mobilizirali s pomočjo G-CSF in jih nato zbrali iz periferne krvi s pomočjo afereze. Vse bolnike smo sledili 5 let.

Rezultati: Ob vključitvi v raziskavo se SC in kontrolna skupina po starosti, spolu, iztisnem deležu levega prekata (LVEF) in vrednosti NT-proBNP nista razlikovali. Ob koncu raziskave je prišlo v skupini SC do pomembnega porasta LVEF (z 24,3 ± 6,5 % na 30,0 ± 5,1 %; P = 0,02), porasta razdalje 6-minutnega testa hoje (z 344 ± 90 m na 477±130 m; P < 0,001) in zmanjšanja vrednosti NT-proBNP (z 2322 ± 1234 pg/mL na 1011 ± 893 pg/mL; P < 0,01). V 5 letih je umrlo 27 bolnikov (25 %); pri 9 bolnikih (8 %) smo opravili presaditev srca. Od 27 smrti je bilo 13 posledica črpalne odpovedi srca, pri 14 bolnikih pa je prišlo do nenadne srčne smrti. Smrtnost je bila manjša v skupini SC (8/55 [14 %]) kot v kontrolni skupini (19/55 [35 %]) (P = 0,01). Zdravljenje z matičnimi celicami je bilo neodvisen napovedni dejavnik preživetja pri multivariatni analizi. (P = 0,04).

Zaključki: Intrakoronarna presaditev matičnih celic omogoča izboljšano delovanje srca, boljšo telesno zmogljivost, zmanjšanje NT-proBNP in izboljšanje preživetja pri bolnikih z neishemično DCM.

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Background

The use of intracoronary bone marrow stem cell (BMC) administration pioneered the field of clinical stem cell therapy more than 10 years ago. Since then, several studies have investigated the role of BMC therapy in various clinical settings, primarily focusing on patients with acute myocardial infarction.[1] Despite the promising short-term results, clinical trials have, however, not consistently shown benefits of intracoronary BMC therapy. Some studies, such as the BALANCE trial,[2] studies of Cao et al.,[3] and the study of Assmus et al.,[4] have shown long-term benefits of BMC therapy in the setting of acute myocardial infarction. The end-points in these studies were a change in left ventricular ejection fraction (LVEF) or combined end-points of myocardial infarction or readmission. In contrast, however, the ASTAMI[5] and the BOOST trial[6] failed to show long term benefits of autologuous BMC therapy. Although the reasons for the differences in long-term outcomes of BMC treated patients with ischemic heart disease remain largely undefined, they may be partially explained by the different degrees of functional exhaustion of BMCs in patients after myocardial infarction.[7]

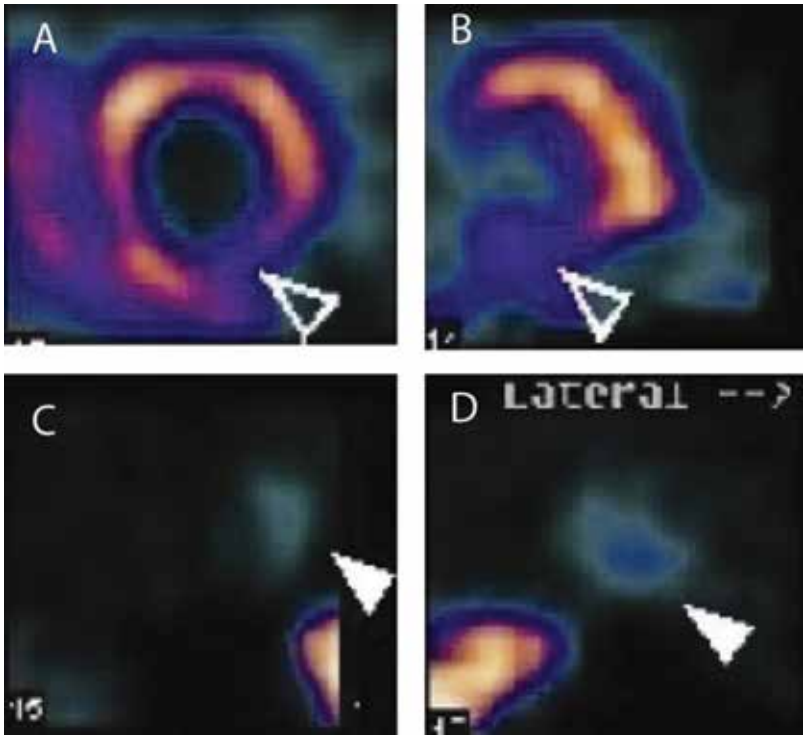

Figure 1: Combined topographic images of myocardial perfusion (A and B) and labeled stem cell scintigraphy (C and D). Decreased perfusion is seen in the inferolateral wall of the left ventricle (arrows) on perfusion images. Accumulation of labeled stem cells can be seen in the lateral and inferior wall, corresponding also to areas of decreased perfusion demonstrated on perfusion scintigraphy (full arrows).

Patients with dilated cardiomyopathy (DCM) have also been shown to have impairment in circulating BMC and endothelial progenitor cells.[8,9] In patients with DCM, lower number of circulating BMC have been associated with worse functional class and increased neurohormonal activation. Despite this, compared to patients with ischemic cardiomyopathy, patients with DCM have higher numbers of circulating progenitor cells with better functional capacity,[10] which could represent a potential advantage for BMC based therapy.

To date, there have only been very few trials investigating the effects of intracoronary BMC therapy in patients with DCM. In the TOPCARE-DCM trial, such therapy resulted in a significant improvement in left ventricular ejection fraction, regional hypokinesia, and N-terminal brain natriuretic peptide (NT- proBNP) at 1 year.[11] In accordance with these findings, the ABCD trial demonstrated an improvement in ejection fraction and quality of life during a mean follow up of 4 years[12]. Previously, in a pilot randomized study, we have found that intracoronary BMC transplantation was associated with an improvement in ventricular remodeling, exercise tolerance and possibly improved survival in these patients[13]. Based on these preliminary data, the aim of the present study is to evaluate long-term effects of intracoronary BMC transplantation in patients with DCM.

Methods

Patient Population

This study consists of an open-label randomized study design conducted at the Advanced Heart Failure and Transplantation Center at the University Medical Centre Ljubljana between May 1st, 2006, and May 1st, 2011, in collaboration with the Methodist DeBakey Heart Center and Stanford University.

Patients with heart failure referred to Advanced Heart Failure and Transplantation Center at the University Medical Centre Ljubljana were considered for inclusion in the study. Inclusion criteria consisted of

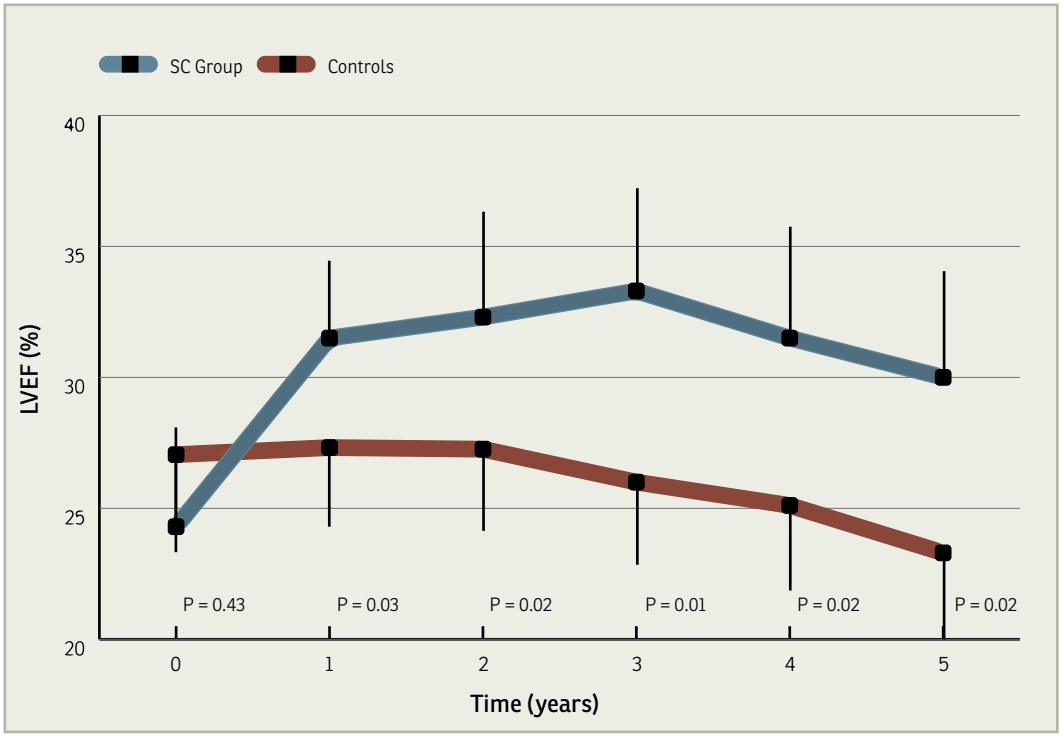

Figure 2: Changes in Left ventricular ejection fraction in stem cell treated patients (SC Group) and Controls. At 1 year, LVEF was significantly increased in the SC group compared to controls, which persisted up to the third year and was still significantly higher at the end of the study.

the following: age 18–65 years, diagnosis of dilated cardiomyopathy according to ESC position statement,[14] optimal medical management for at least 6 months, marked ventricular systolic dysfunction (LVEF < 30 %), and New York Heart Association functional Class III or IV for at least 3 months before referral. Patients with acute multi-organ failure or history of haematologic neoplasms were not included. Informed consent was obtained in all patients before participation in the study, and the study protocol was approved by the National Medical Ethics Committee. The trial was registered in compliance with the Slovenian Medicinal Products Act and with ClinicalTrials.gov (number NCT01350310).

Study Design

In Phase 1 of the study, all patients received granulocyte-colony stimulating factor (G-CSF) therapy to assess bone marrow reactivity and potential effects of G-CSF on cardiac function. Patients, in whom G-CSF therapy was associated with a transient increase in absolute neutrophil count by at least 50 %, were enrolled in Phase 2.

In Phase 2, patients were randomly allocated in a 1:1 ratio to receive intracoronary transplantation of autologous CD34+ cells (SC group), or no intracoronary infusion (control group). At the time of enrollment, and at yearly intervals thereafter, we performed detailed clinical evaluation, echocardiography, 6-minute walk test, and measured plasma levels of NT-proBNP.

Echocardiography and 6-minute Walk Test

The echocardiogram data were recorded and analyzed at 5 years by an independent echocardiographer who was blinded both to randomization and timing of the recordings. LVEF was estimated using the Simpson's biplane method and Teich-Holz technique, and left ventricular end-diastolic dimension (LVEDD) was measured in the parasternal long axis view. Both the LVEF and the LVEDD were averaged over 5 cycles. Similarly, 6-minute walk test was performed by a blinded observer according to the consensus of the American Thoracic Society.

NT-proBNP Measurement

Blood was collected into an EDTA-coated tube containing aprotinin, immediately placed on ice for up to 4 hours, and then centrifuged at 4500 rpm for 15 minutes at 0 °C. The serum was extracted and stored

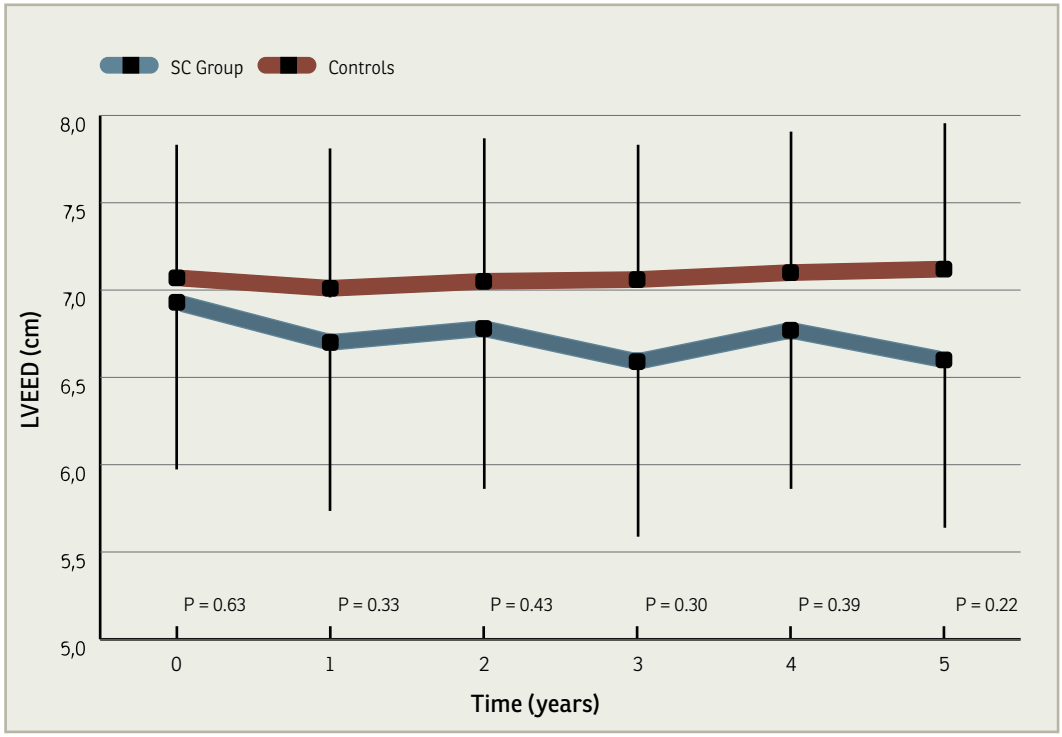

Figure 3: Changes in Left ventricular end diastolic dimension in stem cell treated patients (SC Group) and Controls. No statistical difference for LVEDD at any time point was observed.

at -80 °C until NT-proBNP assay was performed. All NT-proBNP assays were performed at a central independent laboratory, blinded to the clinical data using a commercially available kit (Roche Diagnostics, Mannheim, Germany).

Peripheral Blood Stem Cell Mobilization, Collection and Viability Assesment

Peripheral blood stem cells were mobilized by daily subcutaneous injections of G--CSF (5 mg/kg bid). On the fifth day, a full blood count and peripheral blood CD34+ cell count were performed. Peripheral blood stem cells were then collected with the Amicus cell separator (Baxter Healthcare, IL). The magnetic cell separator Isolex 300i (Nexell Therapeutics Inc, Irvine, CA) was used for the immunomagnetic positive selection of CD34+ cells. In the closed system, the collected cells were washed to remove the platelets, sensitized with mouse monoclonalanti-CD34 antibodies and then incubated with immunomagnetic beads coated with polyclonal sheep anti-mouse antibodies (Dynabeads- Dynal AS, Oslo, Norway). The bead/CD34+ cell rosettes were separated in the magnetic field from other cells and CD34+cells were released from the Dynabeads using an octapeptide with affinity for anti-CD34 antibodies. After immunomagnetic selection, stem cells were assessed for viability using methylene blue and reassessed for viability 2 hours thereafter, before intracoronary injection.

Target Area Selection and Intracoronary Delivery

Before stem cell transplantation, patients underwent myocardial perfusion scintigraphy with 99mTc- sestamibi and nitrate augmentation (Figure 1). Target areas were defined as segments of reduced tracer accumulation and contractile dysfunction. Target coronary artery was defined as one of the major coronary arteries (LAD, LCX or RCA) supplying segments of reduced tracer accumulation on scintigraphy. After full heparinization, a microcatheter (Progreat Microcatheter System, Terumo, Leuven, Belgium) was positioned in a mid-portion of the target coronary artery and the cells resuspended in saline were injected intracoronary. Each patient received 10 injections (10 mL each). To avoid trauma of the target vessel, we performed no balloon inflations at any time during the procedure.

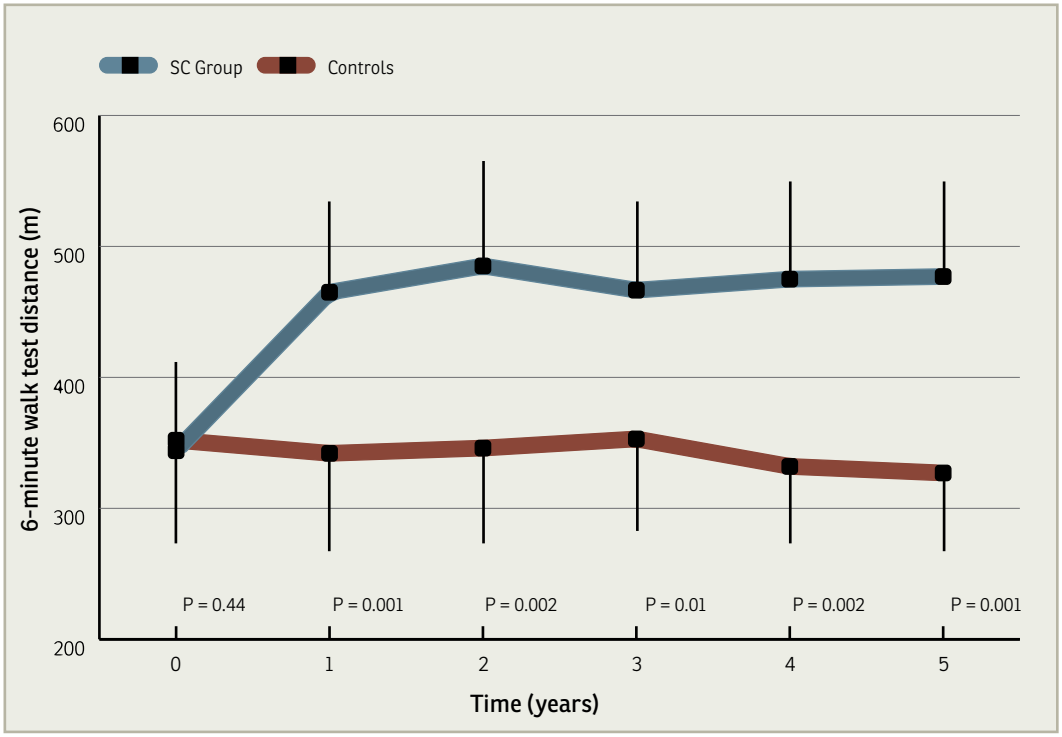

Figure 4: Changes in 6-minute walk test distance in stem cell treated patients (SC Group) and Controls. In the SC group, exercise capacity increased significantly within the first year and remained stable.

Assessment of Myocardial Homing

Before intracoronary injection, a predefined volume (20 %) of stem cell solution was labeled with 99mTc-hexamethylpropylene--amine oxyme (HMPAO). Stem cell solution was centrifuged, supernatant solution was removed and sedimented stem cells were incubated with a solution of 99mTc-labeled HMPAO. After incubation period of 10 minutes, the cells were resuspended and again centrifuged. The average measured activity of stem cell preparation was 150 MBq. Two hours after intracoronary delivery of the cells, stem cell imaging was undertaken to assess myocardial engraftment and distribution. Planar anterior and posterior projections and tomographic imaging of cardiac region was performed on a dual-head gamma camera. After 18 hours, imaging was repeated to detect potential stem cell migration.

Follow-up and End Points

Patients were followed over a period of 5 years. The primary endpoints included changes in LVEF and left ventricular end diastolic dimension. Secondary endpoints included changes in exercise capacity and NT--proBNP levels. In an exploratory analysis, we also compared cardiac death rates, which included sudden cardiac death and death secondary to pump failure. Sudden cardiac death was defined as either a witnessed cardiac arrest or death within 1 hour after the onset of acute symptoms, or an unexpected death in a patient known to have been well within the previous 24 hours.[15] Pump failure death was defined as a death resulting from multi-organ failure caused by heart failure progression. Heart transplantation was performed according to the standard Eurotransplant protocol, which requires each patient to be confirmed by 3 independent auditors.

Statistical Analysis

The minimal sample size for the study was calculated using a pre-specified power of 90 % and P value of 0.05. Continuous variables were expressed as mean±SD. Differences between survivors and patients who died were analyzed by means of 1-factor ANOVA followed by Tukey's test for continuous variables. Comparisons of categoric variables were made by use of the chi-sqare test. Univariate and multivariate stepwise Cox proportional hazard regression analysis were performed to identify independent predictors of sudden cardiac death. The probability value for entering and staying in the model was set at 0.05. The Kaplan-Meier method

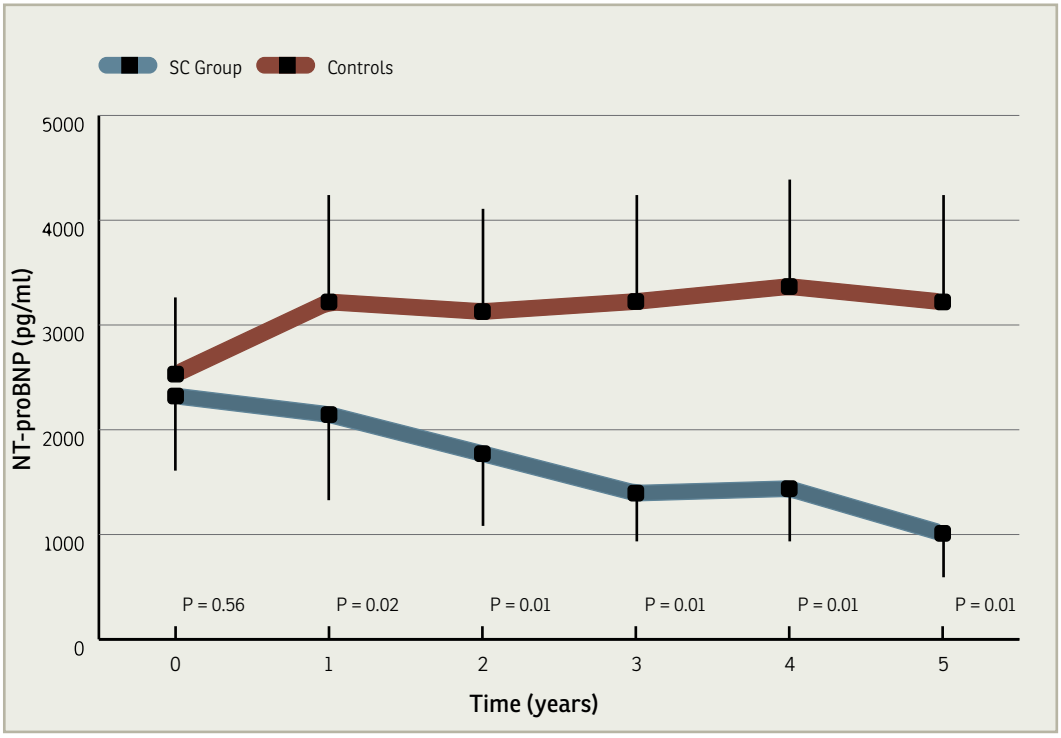

Figure 5: Changes in NT-proBNP levels in stem cell treated patients (SC Group) and Controls. NT-proBNP levels were significant decreased in the SC group at 1 year.

was used to analyze and compare survival in the stem cell group and controls. A value of $P < 0.05$ was considered significant.

Results

Patient Characteristics

Of 131 patients entering Phase 1, we excluded 21 patients because of inadequate neutrophil rise after G-CSF stimulation. The remaining 110 patients were randomly allocated into SC group (n = 55) and control group (n = 55). At baseline, the 2 groups did not differ with regards to age, gender, LVEF, LVEDD, E/Em ratio, plasma sodium, NT-proBNP, or medical management (Table 1).

Stem Cell Delivery and Homing

The average number of intracoronary injected cells was 113 ± 26 million. Average stem cell viability was 91.3 %. Viability of labeled and unlabeled stem cells was 89.9 % and 92.3 %, respectively, and did not differ significantly (P = 0.24).The area of maximal ischemia was variable between patients. Figure 2 illustrates a case where maximal perfusion defects were noted in the infero-lateral and inferior area. In 25 patients, cells were injected in LAD, in 11 patients in LCX, and in 19 patients in the RCA. No cases of distal coronary artery occlusion, acute cardiac dysfunction or significant troponin leak occurred: average plasma troponin I levels were 0.09 ± 0.01 ng/mL at baseline, 0.11 ± 0.02 ng/mL 6 hours after the procedure, and 0.08 ± 0.01 ng/mL 12 hours after the procedure. In 2 cases, patients experienced non-sustained VTs during the procedure.

Using stem cell labeling, we were able to demonstrate successful stem cell engraftment in all patients from the SC group. We found no difference in stem cell retention rates between different target areas at 2 and 18 hours after the procedure (Table 2).

Left Ventricular Function and Dimensions

Time-related changes in LVEF and LVEDD are presented in Figures 2 and 3, respectively. At 1 year, there was an increase in LVEF in the SC group but not in controls, which led to a significant intergroup difference. The improvement of LVEF in the SC group persisted up to the third year; after that it progressively declined. However, when compared to the controls, LVEF at the end of the study still remained significantly higher. Similar results were found when

LVEF was evaluated using Teich-Holz technique . Although there was a trend toward a decrease in LVEDD in the SC group at year 1, we found no statistical difference between the groups at any time point.

Exercise Capacity and NT-poBNP

Exercise capacity in the SC group increased significantly within the first year and remained stable throughout the follow-up period, leading to a significant inter-group difference at the end of the study (Figure 4). In parallel, we found a significant decrease in NT-proBNP levels in SC group at 1 year, which persisted up to 5 years (Figure 5).

Patient Outcome

During follow-up, 27 (25 %) patients died and 9 (8 %) underwent heart transplantation. Of the 27 deaths, 13 were attributed to pump failure, and 14 were attributed to sudden cardiac death. Total mortality was lower in patients receiving SC therapy (8/55, 14 %) than in Controls (19/55, 35 %) (P = 0.01). The same was true of the pump failure (3/55 [5 %] vs. 10/55 [18 %], P = 0.03), but not of the sudden cardiac death (5/55 [9 %] vs. 9/55 [16 %], P = 0.39). Heart transplantation numbers did not differ between the two groups (4/55 [7 %] vs. 5/55 [9 %], P = 0.73) (Figure 6). Five-year survival as evaluated by Kaplan-Meier analysis was 2.3 times higher in the SC group than in controls (P = 0.015) (Figure 7).

Univariate and Multivariate Predictors of Outcome

The results of the univariate and multivariate Cox proportional hazards regression analysis of survival are presented in Table 3. In a model, including baseline LVEF, LVEDD, NT-proBNP levels, and age, stem cell therapy was the only independent predictor of outcome at 5 years.

Discussion

This is the *first* randomized study to date investigating the long-term effects of intracoronary administration of G-CSF-mobilized CD34+ cells in patients with non-ischemic dilated cardiomyopathy. During the

Table 1: Baseline Patient Characteristics

	All (n = 110)	SC Group (n = 55)	Control Group (n = 55)	*P*
Age, y	54 ± 9	53 ± 8	55 ± 7	0.64
Male gender	89 (81)	45 (82)	44 (80)	0.81
LVEF, %	25.2 ± 4.2	24.3 ± 6.5	25.7 ± 4.1	0.40
LVEDD, cm	7.0 ± 0.8	6.9 ± 1.0	7.0 ± 0.7	0.83
E/Em	18.7 ± 7.2	19.1 ± 6.1	18.4 ± 8.3	0.48
Sodium, mmol/l	136 ± 7	138 ± 4	136 ± 9	0.52
NT-proBNP, pg/ml	2390 ± 1974	2322 ± 1234	2431 ± 1995	0.56
Therapy				
Loop diuretics	101 (92)	51 (93)	50 (91)	0.73
Digoxin	20 (18)	9 (16)	11 (20)	0.62
Spironolactone	77 (70)	41 (75)	36 (65)	0.30
RAAS inhibitors	105 (95)	51 (93)	54 (98)	0.17
Beta blockers	89 (81)	43 (79)	46 (84)	0.47

All values, except for P values, represent either mean ± standard deviation or number of patients (%). LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension; NT- proBNP, NT- proB-type natriuretic peptide; RAAS, renin-angiotensin-aldosterone.

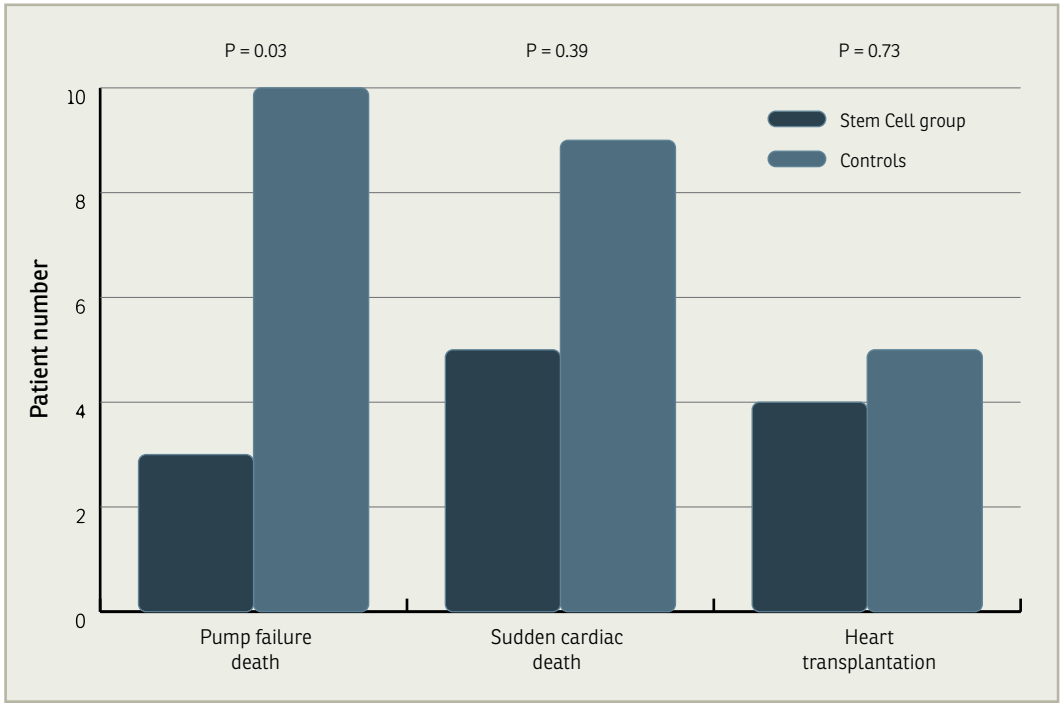

Figure 6: Causes of death in stem cell treated patients (SC Group) and Controls.

5-year follow up, stem cell therapy was associated with a significant improvement in cardiac function and exercise capacity and a significant decrease in NT-proBNP levels. In an exploratory analysis, we also found that total mortality and pump failure death rates were lower in stem cell treated patients; however, we found no effect of stem cell therapy on sudden cardiac death rates.

Based on the current evidence, the underlying mechanisms for our findings are thought to be multiple. In pre-clinical models, it has been shown that BMC administration can improve cardiac function through paracrine effects. These factors can attenuate apoptosis of endogenous cardiomyocytes and endothelial cells,[16] promote angiogenesis, activate resident cardiac stem cells, or induce anti- inflammatory effects.[17] Other studies have also shown that BMCs administration can attenuate the effects of circulating autoantibodies that may be involved in the pathogenesis of dilated cardiomyopathy;[18] this is probably mediated by tolerization of autoreactive T and B cells.

Administration of BMCs could also lead to an improvement in vasculogenesis and angiogenesis. Studies in animal models suggest that implantation of BMCs improves angiogenesis, arteriogenesis, and tissue perfusion as well as left ventricular function.[19] There has been increasing evidence of defective vascularization and impaired vasculogenesis in patients with DCM also.[20] Although the exact underlying mechanisms remain to be defined, they appear to be related to impaired survival of endothelial cells due to increased expression of VE-cadherin/beta--catenin.[21] Myocardial ischemia in patients with DCM could also account for disease progression. Based on similar mechanisms, delivery of CD34+stem cells could improve tissue perfusion and left ventricular function in patients with DCM. In accordance

Table 2: Stem Cell Retention Rates

Time after implantation	Mean	Target Coronary Artery			*P*
		LAD (n = 25)	LCX (n = 11)	RCA (n = 19)	
2 h	7.1 ± 1.5 %	6.9 ± 1.4 %	7.0 ± 1.3 %	7.2 ± 1.8 %	NS
18 h	5.3 ± 1.3 %	4.8 ± 1.5 %	5.1 ± 0.9 %	5.7 ± 1.8 %	NS

All values, except for P values, represent mean ± standard deviation. NS, non significant.

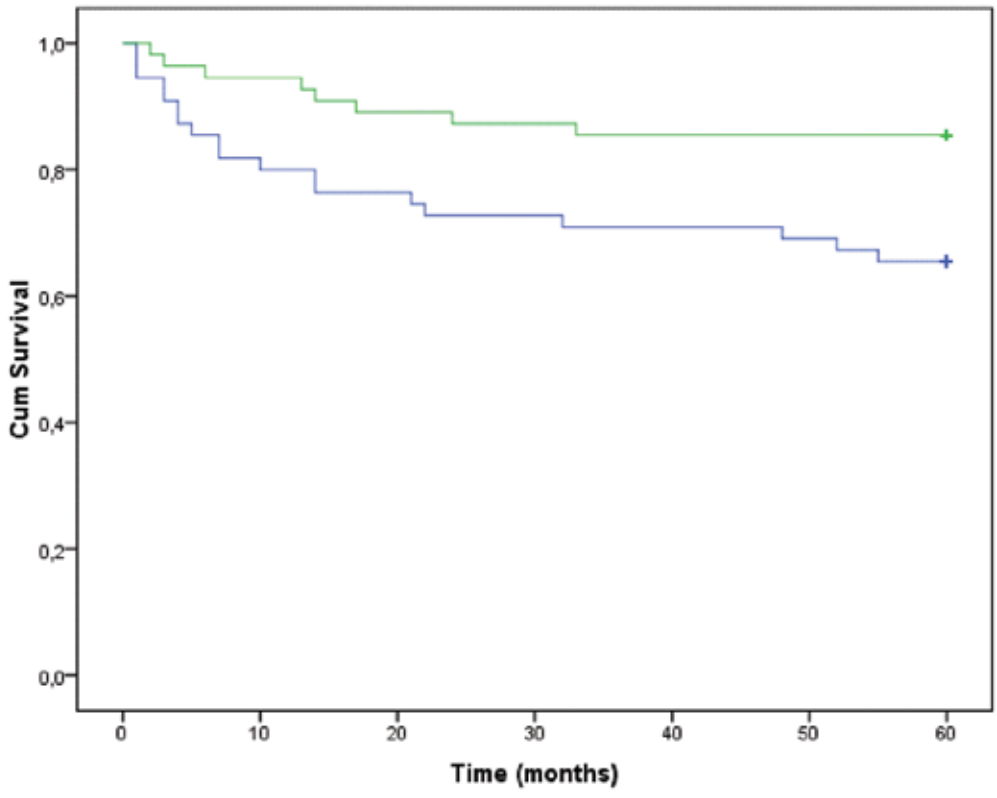

Figure 7: Survival in stem cell treated patients (SC Group) and Controls. Five-year survival as evaluated by Kaplan-Meier analysis was 2.3 times higher in the SC group than in controls.

with this hypothesis, we found that DCM patients exhibit inhomogeneous tissue perfusion on nuclear imaging, which enabled us to select a specific target area for stem cell administration. Using this strategy, we were able to improve myocardial homing of the transplanted cells. Retention rates at 2 and 18 hours were independent from the coronary artery selection (LAD, LCX or RCA), which further proves the validity of this approach.

In the present study, stem cell therapy was associated with an increase in LVEF at 5 years by a mean of 5.7 %. This is comparable to other studies in DCM, which also found an improvement in LVEF in the range of 4–6 %.[11,12] In terms of timing, LVEF improvement appears to occur early after stem cell transplantation (within the first year), and may slowly decrease in the long-term follow up (after the third year). Other studies investigating the long term effects of BMC transplantation also suggest that the beneficial effects of intracoronary BMC transplantation may primarily be limited to the early period after the procedure.[4,6] If further validated, this could suggest that future trials could consider multiple administration of stem cell therapy in patients who decrease their systolic function.

Table 3: Univariate and multivariate predictors of 5-year survival

	Univariate	Multivariate	95 % Confidence Interval	
	P	Hazard Ratio		*P*
Stem cell therapy	0.04	3.4	1.05–5.77	0.04
NT-proBNP< 1000 pg/ml	0.03	-	-	-
LVEF> 20 %	0.05	-	-	-
Age< 60 years	0.08	-	-	-

LVEF, left ventricular ejection fraction; NT- proBNP, N-terminal brain natriuretic peptide.

As previous studies have shown, BMC transplantation was not associated with significant change in left ventricular size in our study.[11,12] This may suggest that BMCs may improve myocardial function to a greater extent that structural remodeling. In preclinical models, improvement in myocyte function was primarily associated with improved tissue perfusion;[22] this could represent the underlying mechanisms of improvement in ventricular function in our study. It could also explain why BMC transplantation may be beneficial in DCM without directly leading to novel myocyte generation. The beneficial effects on ventricular function were also reflected by improvement in NT-BNP levels by more than 50 % and by improvement in exercise tolerance. The time course of these changes correlated with changes in LVEF, with the majority of the improvement occurring within the first year. Taken together with the findings of TOPCARE-DCM trial,[11] these results suggest the long-term beneficial effects of BMC therapy in DCM patients.

In our exploratory analysis, we have also found a significantly lower mortality rate in patients receiving stem cell therapy as compared to the controls, the difference being largely a consequence of reduced pump-failure death rates. This suggests that improvement in left ventricular function after stem cell therapy also translates in long term clinical benefits. The positive effect of stem cell therapy on mortality was evident primarily within the first year, which strongly correlates with the time course of other clinical parameters in this study. We found no effect of stem cell therapy on sudden cardiac death rates but the study was underpowered to this effect. A previous study from our group has shown, however, that stem cell therapy does not significantly affect parameters of ventricular repolarization.[13] In contrast to some other more undifferentiated cell types, BMCs have been proven several times not possess an arrhythmogenic potential;[1] a finding consistent with the results of our study.

Study Limitations

The results of our study are subject to several limitations. Although our patient population included patients with dilated cardiomyopathy, no biopsies were performed to exclude secondary cardiomyopathies. Our sample size was small and the study was underpowered for analysis of mortality. Because of a pilot study design, the study was not placebo-controlled or double-blinded. To minimize this potential bias, echocardiographic and exercise capacity evaluation were performed by independent observers blinded to the patient grouping.

Although we found no effect of cell labeling on viability assessed by methylene blue staining, we have not measured cell proliferation and migration parameters to verify that the nuclear tracer had no effect on the cells. Finally, we recognize that patients with dilated cardiomyopathy are a heterogeneous patient population and dynamic changes in ventricular function may be multi-factorial.

Conclusions

Intracoronary transplantation of autologous CD34+ cells appears to be a safe treatment modality in patients with DCM. Our results suggest long-term improvement in cardiac function and exercise tolerance, and a decrease in NT-proBNP, which may translate into improved outcome of this patient cohort. Most of the benefits of the therapy were observed within the first year, which may serve as a background for potential repeated stem cell transplantation in selected patients.[23] Further studies are needed to better define the underlying mechanisms, improve stem cell homing, and further improve the outcome of patients with non-ischemic dilated cardiomyopathy.

Disclosures

None.

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