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Review article

Direct Injection of Embriofetals Stem Cell (Hfdscs) in Heart Failure Patients is Time to Repeat

Federico Benetti[1,2], Natalia Scialacomo[1,2], Bruno Benetti[2]

[1] Cardiac Surgery Department Cardiac Surgery, Benetti Foundation, Alem 1846 Rosario, Argentina

[2] Department of Regenerative Medicine, Benetti Foundation, Alem 1846 Rosario, Argentina

*Corresponding author: Federico Benetti MD, Cardiac Surgery Department Cardiac Surgery, Benetti Foundation, Alem 1846 Rosario, Argentina

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Abstract

Thirteen years ago we did a trial to investigate the safety and efficacy of embriofetal cells (HFDSCs) implantation for the treatment of idiopathic cardiomyopathy. The improvement seen in these trials suggests that HFDSCs have some therapeutic effect. The mechanism of action, has seen via echocardiographic imaging, suggests, that the increased wall thickness and contractility in the regions described and the decrease of diastolic diameter the might be due to an increase in the number of new cardiomyocytes. These in findings suggest, however, that HFDSC transplantation improves cardiac function in HF patients at 40 months. No rejection reactions or malignancy has been seen in none of the patients follow up cells After 13 years and the actual evidences of the different stem cells treatments in HF and do to the positives evidences we have in this first trial , is time to do a phase III, trial with HFDSCs and more number of patients to confirm the initials observations.

Keywords: embriofetal cells in hear failure, stem cells in heart failure, surgical implantation of stem cells, embriofetals cells heart application

Introduction

Chronic heart failure (HF) represents an increasingly common and debilitating disorder worldwide and carries a dismal prognosis and is related to unacceptably high mortality rates [1]. Although current HF treatment options have been shown to improve HF symptoms and signs, to reduce heart failure-related hospital admissions, and above all to improve patients' survival [2], no therapeutic modality to date has addressed the repair of damaged/lost myocardial tissue Cardiac transplantation is currently the only established surgical treatment for refractory end-stage HF (stage D), but it is available to fewer than 4000 patients in the United States each year. Human fetal-derived stem cells (HFDSCs) are thought to be more pluripotent than adult stem cells; the former can develop into a wider range of specialized cells [3]. In 2005 we did the first surgical trial to investigate the safety and efficacy of HFDSC implantation for the treatment of idiopathic cardiomyopathy [4].

Methods

This investigation was an open-label, single-arm, prospective clinical study performed at Luis Vernaza Hospital, Guayaquil, Ecuador. The study was approved by the Ethics Committee of the hospital, and prospective participants were fully informed about the potential risks of the surgical procedure and HFDSC transplantation. Informed consent was obtained from all patients.

Patient Population All patients were assessed at baseline with respect to biochemistry profile, complete blood count, coagulation profile, electrocardiogram, chest radiograph, transthoracic echocardiogram with a Vivid 7 device (GE Healthcare, Piscataway, NJ, USA), cardiac catheterization with coronary angiography to exclude ischemic heart disease, a 6-minute walk test over a 30-m fl at surface, an exercise tolerance test (ETT) according to a modified Naughton protocol, NYHA classification, and a Minnesota congestive HF test. Patients participating in

the study met the following inclusion criteria: American Heart Association diagnostic criteria for dilated nonischemic, nonchagasic cardiomyopathy; an EF ≤35% by transthoracic echocardiography; a NYHA functional class of III or IV; bilirubin, creatinine, blood urea nitrogen, serum glucose, glutamic-oxaloacetic transaminase (aspartate aminotransferase), and glutamic pyruvic transaminase levels <2.5 times normal values; and a symptomatic condition despite optimal drug therapy for HF.

Exclusion criteria included the following: valvular heart disease requiring surgical treatment; other concurrent life threatening disease, infectious disease, blood disease, diagnosis of epilepsy, or positivity in human immunodeficiency virus or Venereal Disease Research Laboratory testing; intolerance or hypersensitivity to biological substances; participation in another clinical trial; a history of drug or alcohol abuse, psychiatric disturbances, or suicide attempts in the previous 2 years; renal failure needing dialysis; a white blood cell count <5000/μL or >12,000/μL, a hematocrit <30%, or pulmonary thromboembolism within the previous 6 months; mechanical ventilation support within the previous 10 days; and morbid obesity.

Patients who were initially included but who were noncompliant with the protocol (tests or treatments), were lost to follow-up, or developed an unrelated new illness were excluded from the study. For each patient, preoperative medications (digoxin, furosemide, spironolactone, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers) were maintained throughout the study and the follow-up.

Stem Cells HFDSCs were provided by the Institute for Regenerative Medicine, Barbados, and were processed and prepared by the Institute for Problems of Cryobiology and Cryomedicine (IPCC) (Kharkov, Ukraine). The IPCC obtains HFDSCs from fetuses of 5 to 12 weeks' gestation from legally consenting, noncompensated donors who have undergone terminated ectopic pregnancies, elective abortions, or spontaneous miscarriages. The HFDSCs are prepared from harvested fetal liver tissue under sterile conditions and undergo polymerase chain reaction testing for human immunodeficiency virus, hepatitis B and C, mycoplasma, toxoplasmosis, cytomegalovirus, herpes simplex viruses I and II, rubella, and Treponema pallidum; HFDSCs also undergo culture tests for bacterial and fungal contamination.

Cell preparations are stored in cryopreservatives at –196°C in liquid nitrogen. The percentage of viable cells was 60% according to the IPCC certification. The IPCC shipped HFDSCs in minishipper containers in a cyropreserved state (–150°C to –196°C) to the Hospital for this study, and they were maintained in this state until use. Just before the procedure, HFDSCs were thawed to room temperature. In 9 patients, the cells were diluted in 80 mL of saline solution at 37°C; in 1 patient who underwent the procedure via a minithoracotomy approach, the cells were diluted in 15 mL. Each patient received 60 to 80 × 106 HFDSCs, according to the information issued by the provider.

Anesthesia and Surgical Technique Patients were anesthetized with 0.50 μg/kg fentanyl as a premedication, with 2 mg/kg thiopental as induction, with 1 mg/kg atracurium for relaxation, and with 0.025 μ g/kg per minute of remifentanil and 0.5% to 1.5% sevofurane for maintenance during the procedure.

Nine patients underwent a midline sternotomy, and 1 patient had a left anterior minithoracotomy in the fifth intercostal space off pump. Prior to the injections, 80 marks (1 cm apart) were made with a blue methylene marker on the anterolateral, posterolateral, and diaphragmatic left ventricular walls and on the anterolateral right ventricular wall, with care taken to avoid coronary blood vessels. We administered 80 injections of 1 mL each in the marked areas. The injections were made 3 mm deep with a 25-gauge needle and a catheter. Only 15 injections were made in the anterolateral wall in the patient who underwent the minithoracotomy (S.B., female, 48 years). During the procedure, patients were monitored for arterial pressure, central venous pressure, urine output, electrocardiogram, oxygen saturation, and endtidal carbon dioxide concentration in the expired air. Infusions of potassium (20 mEq/hour) and magnesium (1 g/hour) were started before the operations and maintained up to the time of chest closure. All patients were extubated in the operating theater. At 40 months after the procedure, each patient underwent reassessment for NYHA classification, an ETT, the EF, the left ventricular end-diastolic dimension (LVEDD), and performance in a 6-minute walking test. The Minnesota congestive HF test was performed before the operation and at 40 months. Statistical Analysis Mean values for parameters measured just before and after the procedure were compared with paired Student t tests (Primer program; Primer-E, Ivybridge, UK).

Results

Six female and four male patients (age range, 47-77 years) met the inclusion criteria and participated in the study. There was no operative or perioperative mortality. One male patient (U.J., 69 years) experienced a single transient intraoperative ventricular fibrillation during the procedure but before receiving injections; the ventricular fibrillation was terminated by electrical cardioversion. One man (M.J., 66 years) and one woman (V.M., 77 years) required temporary pacemakers postoperatively

Table 1. Statistical Analysis Mean values for parameters measured just before and after the procedure were compared with paired Student t tests (Primer program; Primer-E, Ivybridge, UK).

Improvement in patient characteristic from Baseline at 40 months following human fetal-derived stem cell transplantation*.				
Result				
Variable	Before Transplantation	40 Months Postoperatively	Change	*p*
NYHA class	3.4±0.5	1.33±0.5		.001
Ejection fraction, %	26.6% ±40%	34.8%±7.2%	31%↑	.005
ETT, min	4.25	16.63	291.3%↑	<.0001
ETT, METS	2.46	5.63	128.9%↑	
LVEDD, cm	6.85±0.6	5.80±0.58	15%↑	<.001
6-MWT,s	251±113.1	360±0	43.2%↑	.01
Mean distance, m	284.4±144.9	468.2±89.8	64.4%↑	.004
Minnesota CHF test	71±27.3	6.0±5.9		<.001

*Data are presented as the mean ± SD where indicated, NYHA: New York Heart Association; ETT: excerise tolerance test; METS: metabolic equivalents ; LVEDD: left ventricular end-diastolic dimension; 6-MWT: 6-minute walk rest; CHF: congestive heart failure.

because of severe bradycardia (<40 bpm), for 24 hours and 48 hours, respectively. The former patient received dobutamine for 24 hours. He also had a mild pericardial effusion at 3 weeks, which resolved spontaneously. He was later excluded from the trial for noncompliance (he abandoned his controls), and he ultimately died at 5 months. The heart autopsy showed nests of cardiomyocytes among the fibrotic tissue, but it was not possible to determine whether they were new growing myocardium or remaining native fibers.

One female diabetic patient (Q.A., 52 years) had a right hemiparesis 3 days after implantation due to ischemic stroke that was confirmed by computed tomography scanning. Although the patient was alive and recovering as of this writing, she was excluded from the protocol because she was unable to perform the follow-up tests of the study. She died 18 months after the procedure from diabetes complications. Another female patient (B.M.) was hospitalized 3 times (at 2, 4, and 7 months postoperatively) because of abdominal pain caused by severe gastroenteritis that led to transient decompensation. She therefore required inotropic support with dobutamine for 48, 48, and 72 hours, respectively. Although no improvement in her EF was noted at 210 days postoperatively, there was a significant improvement in her ETT performance, the LVEDD, and her performance in the 6-minute walk test. At the 210-day follow-up, no other complications were observed. The patient died suddenly at 8 months postoperatively. The female patient who underwent her procedure via mini thoracotomy died at 12 months from HF caused by a mitral insufficiency. She had refused a mitral valve operation. The patients who provided 40 months of follow-up data demonstrated improvements both clinically and in imaging studies. With regard to the imaging studies, we noted an increased wall thickness, both eccentric and concentric.

Patients improved in association with increased contractility in these regions. Compared with baseline assessments, we noted other improvements: The mean (±SD) NYHA class decreased from 3.4 ± 0.5 to 1.33 ± 0.5 (P = .001); the mean EF increased 31%, from 26.6% ± 4.0% to 34.8% ± 7.2% (P = .005); performance in the ETT increased 291.3%, from 4.25 minutes to 16.63 minutes (128.9% in metabolic equivalents, 2.45 to 5.63) (P < .0001); the mean LVEDD decreased 15%, from 6.85 ± 0.6 cm to 5.80 ± 0.58 cm (P < .001); mean performance in the 6-minute walk test increased 43.2%, from 251 ± 113.1 seconds to 360 ± 0 seconds (P = .01); the mean distance increased 64.4%, from 284.4 ± 144.9 m to 468.2 ± 89.8 m (P = .004); and the mean result in the Minnesota congestive HF test decreased from 71 ± 27.3 to 6 ± 5.9 (P < .001) (Table). The Kaplan-Meier probability of survival at 40 months was 66% .One patient died at 11 years of follow up and another patient is alive and asymptomatic at 13 years the rest were lost of follow up.

Conclusion

The findings from the first study of the application of embriofetals stem cells therapy in HF patients showed

statistically significant improvement in left ventricular function (EF and LVEDD), NYHA class, and performance in the ETT, the 6-minute walk test, and the Minnesota congestive HF test at 40 months after direct implantation of embriofetals cells. All patients were maintained on their preoperative medications and dosages throughout the study. It is worth noting that no new recurrent or permanent arrhythmias were seen after implantation in this surgical series of patients.

Studies have found arrhythmias in patients with HF or myocardial infarction who were given skeletal myoblast cell therapy, but this complication appears to be less of a problem with autologous and others adult stem cells We believe that the sustained effect of HFDSC therapy indicates that it offers another possibility for treating patients with advanced HF and represents a new approach that could be used before other major surgical treatments, including heart transplantation, by having them available "on the shelf," thereby avoiding the time-consuming procedures of harvesting and processing. The stem cells After 13 years and do to the differents results of stem cells treatments in HF and with the evidences we have in this first trial, is time to do a phase III, trial with HFDSCs and more number of patients to confirm the initials observations.

Disclose

The authors have nothing to disclose.

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