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Review Article

Surgical Fetal Stem Cell Transplant into Heart Failure Patients Long-term Results at 14 Years

Federico Benetti[1]*, Luis Geffner[1], Yan Duarte[2] and Ernesto Peñaherrera[2]

[1]Benetti Foundation, Argentina

[2]Hospital Luis Vernaza, Guayaquil, Ecuador

Abstract

Direct myocardial transplant of HFDSCs (human fetal derived stem cells) by open chest surgical procedure was performed in 10 patients with Heart Failure (HF) due to no ischemic, no chagasic dilated cardiomyopathy. All 10 patients survived the operation. At 40 months, 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% ± F) 34.8% ± 7.2% (p = .005); and the mean ETT increased 291.3%, from 4.25 minutes to 16.63 minutes (128.9% increase in metabolic equivalents, from 2.46 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 by 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 test decreased from 71 ± 27.3 to 6 ± 5.9 (p < .001). Six patients survived after 40 months; 5 of them had complete reverse remodeling after 3 months after transplants. The average age at the moment of the transplants was 62 years (s/d 11.6).

Results: The first patient died at 5,4 years for an infection; the second patient died at,7,4 years for heart failure; the third patient died at 8,4 years for heart failure; the fourth patient died at 10 years for heart failure and the fifth patient died at 14,4 years after transplant at the age of 83 for heart failure. The average age at the moment of death was 70 years (s/d12.9). The survival rate at 4 years was 100% (K/M) and at 14 years (25%K/M).

Conclusion: These initial worldwide experiences with the surgical direct transplant of liver fetal stem cells in patients with end-stage HF shows clearly the positive effect in the reverse remodeling of the left ventricle of 50% of the cohort and excellent long-term results in these types of patients opening a new avenue for treating end-stage HF patients without any other option of treatment.

More Information

***Address for correspondence:** Federico Benetti, Benetti Foundation, Alem 1846 Rosario Santa Fe Arg zip 2000, Argentina, Email: federicobenetti@hotmail.com

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Introduction

Congestive Heart Failure (CHF) is one of the main causes of cardiologic morbidity and mortality in the twenty-first century [1,2]. Patients in advanced stages of CHF (NYHA functional classes III/IV) have 5-year survival rates that average below 50%, with an annual mortality of 40% – 50% [3], including high rates of re-hospitalization, morbidity, and complications, and high related costs for health services. The etiology of dilated cardiomyopathy comprises 60% that are due to ischemic cardiomyopathy and 40% that are of idiopathic, non-ischemic origin.

The idiopathic category of CHF patients has been managed with medical treatment (ACE inhibitors, diuretics, beta-blockers, Spiro lactone), ventricular re-synchronization, ventricular assistance, and heart transplantation. For many years, heart transplantation has been the surgical treatment of choice for patients with advanced CHF. This procedure has been successful in many countries; however, it presents many limitations, the most important ones being the scarcity of suitable donors and the contraindications of advanced age and severe co-morbid situations [4]. Moreover, there have been frequent deaths during the prolonged periods that patients remain on the waiting list for organ reception.

The final stage of several heart diseases ending in CHF is the quantitative deficiency of cardiomyocytes and cardiac remodeling [5]. The theoretical potential for reversion of cardiac remodeling lies in the possibility of myocyte

regeneration and neo-vascularization of affected areas. The ultimate goal of cellular therapy is the re-population of the myocardium with cells capable of restoring blood flow as well as cells capable of restoring contractility. This will improve the system-diastolic function of the heart. The cells introduced must have the capacity for differentiation into cardiomyocytes or to promote revascularization.

Several studies have shown that the adult bone marrow is a rich reservoir of pluripotential mesenchymal stem cells, which contribute to functional neo-angiogenesis. They also participate in wound healing and reversion of lower limb ischemia [6], post–MI neo-angiogenesis [7,8], endothelialization of vascular grafts [9], atherosclerosis [10], retinal and lymphoid neo-vascularization [11] and vascularization during neonatal development [12]. among others Although more recent investigations showed possibilities of treatment with other stem cells apart from the fetal cells used in our work it is clear that more research is needed in these different stem cell implantation in patients with Heart failure to consider the use of them in clinical practice [13-17].

We already determined the efficacy and safety of HFDSC treatment in CHF patients [18]. In this study we demonstrate the efficacy of these cells in patients with reverse remodeling of the left ventricle from 3 months after the transplant up to 14 years of follow-up. Although we recognize that a larger cohort of patients NYHA class III-IV should be treated with HFDSC to confirm these initial positive results.

Methods

In January 2005, the ethical committee of the Luis Vernaza Hospital, Guayaquil, Ecuador approved the class I/II prospective study for transplanting human fetal stem cells in 10 patients NYHA class III/IV due to idiopathic myocardiopathy with no other options but full clinical treatment. Heart transplants, temporary or permanent assisting devices, or artificial heart no were available in Ecuador at that moment. The economic and medical situation made it impossible to send this particular group of patients to be treated in other countries.

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 volunteer participants were fully informed about the potential risks of the surgical procedure and HFDSC transplantation. Informed consent was signed by all the patients,

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, non-compensated 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 e 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 mini-shipper containers in a cryopreserved state (–150 °C to –196 °C) to Luis Vernaza Hospital for this study, and they were maintained in this state until use. Just before the procedure, HFDSCs were thawed to room temperature. The cells were diluted in 80 mL of saline solution at 37 °C; each patient received 60 to 80 × 10^6 HFDSCs, according to the information issued by the providers. Injections were performed on the beating heart in all the heart surfaces of the left ventricle and part of the right ventricle. The initial results at 40 months of this study showed promissory results [18] of this initial group. Five patients, 2 women and 3 men with an average age of 62 (s/d 11, 6) showed reverse remodeling of the left ventricle after the surgical transplant of HFDSC and were followed for 14 years.

Results

Initially, all 10 patients survived the operation. At 40 months, 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% to 34.8% ± 7.2% (p = .005); and the mean ETT increased 291.3%, from 4.25 minutes to 16.63 minutes (128.9% increase in metabolic equivalents, from 2.46 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 by 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 test decreased from 71 ± 27.3 to 6 ± 5.9 (p < .001) 6 patients survived after 40 months. Five of them showed complete reverse remodeling after 3 months of implantation [18]. The first patient died at 5.4 years of infection; the second patient died at 7.4 years due to heart failure; the third patient died at 8.4 years, also due to heart failure; the fourth patient died at 10 years because of heart failure and the fifth patient died at 14.4 years after transplant at the age of 83 due to heart failure. The average age at the moment of death was 70 years (s/d12.9). The Survival rate at 4 years was 100% (K/M) and at 14 years (25%K/M).

Discussion

When faced with different stimuli, such as parietal stress

or direct myocardial injury leading to hemodynamic overload, the heart responds with hypertrophy, which is capable of initially compensating for loss of function. Later on, and for a long sub-clinical period, progressive dilatation continues to be compensated by varying degrees of hypertrophy. At the final stage, as described by Meerson, et al. [19], dilatation exceeds hypertrophy, and changes in cellular organization appear, such as 1) myofibrillar lysis; 2) increase of lysosomes; 3) distortion of the sarcoplasmic reticulum; 4) substitution of myocardial cells by fibrous tissue. Simultaneously, capillary density and contractile reserve decrease. In addition, diffuse myocytic necrosis is a feature of both idiopathic and ischemic dilated cardiomyopathy [20,21]. Therefore, idiopathic dilated cardiomyopathy can be described from a pathologic point of view [22] as a dilated heart with hypertrophied walls. Macroscopically, dilatation exceeds hypertrophy; microscopically the heart appears invaded by areas of interstitial and perivascular fibrosis, adjacent to necrotic areas and areas containing myocytes that may be atrophic or hypertrophic, with loss of extracellular matrix. Cellular therapy in these patients is directed to restore and repopulate the myocardium, thus attempting to recover the lost function by the delivery of cells that can induce neovascularization and also differentiate into myocardial cells.

The use of mesenchymal or stromal stem cells as precursors of non-hematopoietic tissues was attempted for the first time by the German pathologist Conheim in 1867 [23]. Either bone marrow-derived stem cells, mesenchymal stroma cells, or Mesenchymal Stem Cells (MSC) maintain stable expression of a major set of markers: CD29, CD44, CD45, CD73, CD90, CD105, CD146, CD166, and less than 5% CD271 and negative for CD34 [24]. HFDSC has been used in this study, characterized as a CD34-positive cell population. Also, this type of cell is positive for markers CD45 and CD90/Thy1 [25]. This represents hepatic differentiation of the foregut endoderm. The cellular responses to inductive signals evolve a new pattern of gene expression sets that are required for cell differentiation. It was later shown in tissue culture studies that these cells were capable of forming micro anatomically diverse tissues, such as bone, cartilage, muscle, ligaments, tendons, etc [23,26] and of intervening in tissue repair [26]. That is why they have been referred to as stem cells. An extremely interesting study showed that stromal stem cells treated with 5-Azacytidine and injected together with cardiomyocytes interconnected with the latter after one week, forming microtubules. After 2 weeks they began beating, and this contraction became synchronous after three weeks. They produced natriuretic peptides and could be stained with antibodies against actin and myosin, and also presented an action potential characteristic of cardiac cells [26].

The trans-differentiation into the cardiac phenotype requires an adequate microenvironment. Dependence on cellular interconnection by generating cardiac transcription factors (GATA-4 and myocytic factor 2) was also observed [27]. This last point was confirmed by other researchers, stressing the importance of cardiomyocyte intercellular integration with trans-differentiated cells [28,29]. Among the various cell types studied, stromal stem cells were shown to have the capacity for differentiation into muscular and vascular cells, and the capacity to produce neo-vascularization. The first reported case of BM cells applied to cardiomyoplasty was by Yau, Tomita and Weisel of Toronto University in 1999 [30]. The differentiation into a myogenic lineage with the development of actin, myosin and tropomyosin was demonstrated, as well as the presence of Connectin 43, a protein responsible for cellular interconnection.

Several mechanisms of stem cell action on improving cardiac function have been proposed [31]:

1. **Fusion and trans differentiation:** Simple stem cell fusion with local cardiac cells has been ruled out, and the attractive concept of stem cells trans-differentiating and crossing the barrier has yet to be demonstrated. Perhaps the correct anatomical mechanism will be clarified in cases where cell therapy can be used as a bridge for heart transplantation and biopsies can later be performed on the original treated heart tissue.

2. **Cardiac stem cell mobilization:** Another theory proposes that the implanted cells mobilize specific cardiac stem cells lodged in the muscle that are capable of cardiac regeneration.

3. **Angiogenesis:** The transplanted cells induce significant angiogenesis; according to some authors this could be the main therapeutic mechanism involved.

4. **Extracellular matrix:** In heart failure, there is a net loss of myocytes plus a loss of matrix architecture, which is related to the etiology of dilatation. The implanted cells could help stabilize the matrix architecture, preventing dilatation and balancing generation/degradation enzymes.

Regarding the patients transplanted with HFDSC, we recognize that the shortage of this cohort in this study may represent a significant limitation in interpreting the results. Nevertheless, these initial findings suggest that HFDSC transplantation improves cardiac function in HF patients for up to 40 months [18]. No rejection reactions or any evidence of malignancy have been seen up to 14 years of follow-up. 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 or instead of other major surgical treatments, including heart transplantation, by having HFDSC available on the shelf in the treatment center, thereby avoiding the time-consuming procedures of autologous bone marrow

harvesting and processing. Irrespective of the clinical improvement seen in this trial, it is still premature to try to define the mechanism of action, indications, or optimum therapeutic doses for HFDSC injections,

On the other hand, there may be potential for further development of HFDSC therapy in combination with other complementary efficacious approaches. For example, it has been shown in an experimental model that Basic Fibroblast Growth Factor (bFGF), applied via a slow-release system based on gelatin hydrogel encapsulation, can enhance survival and number/volume of transplanted fetal myocardial cells that survive post-application in the case of ischemic cardiomyopathy. As a result, the combined therapy significantly enhanced the improvement in postoperative cardiac function [32,33]. It has also shown that bFGF slow release can provide similar benefits to transplanted fetal myoblasts [34] and adult bone marrow-derived mononuclear cells.

One of the merits of bFGF slow release by gelatine hydrogel is that it does not increase systemic blood levels of bFGF. It acts as a local therapy, and should therefore have fewer side effects and meet stringent safety criteria. This approach uses no genes (neither DNA nor RNA), nor any viral vector [35,36] to achieve this local (analogous to paracrine) growth factor effect. This approach has also been shown to be safe and effective in human clinical trials [36-38], to induce small arteries as opposed to capillaries, in contradistinction to VEGF [39] and is compatible with minimally invasive techniques [40] such as mini-thoracotomy. The combination of growth factor therapy with cell therapy, especially bFGF with HFDSC, is an option to try to improve stem cell approaches to the successful treatment of idiopathic cardiomyopathy.

Stimulation of injected HFDSCs, which may also be considered hepatoblasts, to transdifferentiation, continues under the influence of a variety of cytokines and growth factors secreted by mesenchymal cells in the septum transversum, such as mentioned above, including bFGF, Epidermal Growth Factor (EGF), Hepatocyte Growth Factor (HGF), Transforming Growth Factor (TGF)-β, Tumor Necrosis Factor (TNF)-α, and interleukin-6 (IL-6) [41]. All of these features make this type of cell valuable for transplantation and tissue regeneration. Although more recent investigations show possibilities of treatment with other stem cells apart from the fetal cells used in our work it is clear that more research is needed on these different stem cells implantation in patients with Heart failure to consider the use of them in clinical practice [13-17]. Unfortunately, controversy and ethical issues are encountered to use human fetal cells but due to our initial experience and the observations that we saw this type of cells produce new heart cells [18]. The survival rate of 100% at 4 years and 25% at 14 years in the group of patients in which the cells produced reverse remodeling at 3 months after the transplants opens a new option in the treatment of these patients. It is clear that we need to perform another trial with more patients with HFDSC to confirm these initial positive findings since abortion on request is legal in many countries and donation of tissues is allowed.

Conclusion

These initial worldwide experiences with the surgical direct transplantation of HFDSC in patients with end-stage HF and no other option shows clearly the positive effect in the reverse remodeling of the left ventricle of 50% of the patients and excellent long-term results opening a new avenue for the treatment of end-stage HF patients. We recognize that a larger cohort of patients with NYHA class III-IV should be treated with HFDSC to confirm these initial positive results.

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