

Are There Scientific Evidences that the Stem Cell Use is Benefic to Patient with Dilated Cardiomyopathy?

REVIEW

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Abstract

Background: The dilated cardiomyopathy (DCM) is one of the most important causes of cardiac insufficiency, leading to morbidity and mortality augment, due to therapeutic restriction.

Objective: To search scientific evidences about the treatment of dilated cardiomyopathy with stem cells use.

Results: The stem cells use in this pathology has shown benefits through human and animals experiments, verified through images and laboratorial exams.

Conclusion: Even with positive results, this treatment requires deeper studies that can show consistent vantages of this therapy in humans.

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Keywords

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The dilated cardiomyopathy is a structural cardiac alteration by cardiomyocytes alteration, resulting in a cardiac contractility impairment, and, consequently, in cardiac insufficiency [1]. Morschbacher et al., (2016) [2] highlighting Nagaya et al., (2015) [3], demonstrated that, besides the cardiomyocytes alteration, there is an augment in the fibroblast number, which is another mechanism of cardiac insufficiency development. Despite the advances in medical area,

the cardiac insufficiency continues to presents high morbidity and mortality taxes.

Haddad et al., (2015) [4], highlighting the concepts of Hunt et al., 2009 [5], have observed that almost 50% of the patients with advanced cardiac insufficiency are submitted to cardiac transplant or to mechanic circulatory support, and the stem cells therapy is presented as a promise to these patients.

The justification for this goal is that this therapy performs a cardiomyocytes repair, leading to an augment of growth factors and cytokines, which diminishes the local inflammation, mitigating the progression of dilated cardiomyopathy and the left ventricle remodeling [6].

In a recently published study performed in Stanford University, 37 patients with long-term dilated cardiomyopathy, from January 3 of 2011 to March 5 of 2012, left ventricular ejection fraction (LVEF) < 40% and Classification in New York Heart Association (NYHA) III, were submitted to intramyocardial injections of stem cells, tagged with Technetium-99m to evaluate the retention after 18 hours [4].

The echocardiogram, NT-proBNP and GGT dosage and walking test were performed, and then the cytokines network 3 months after the application was compared. The response was definite, with an augment of LVEF $\geq 5\%$ in 3 months. There was reduction of several cytokines and inflammatory markers levels, however, there was no significant difference in LVEF and in NT-proBNP. There was, however, a significant difference in GGT levels. Besides, the premature retention resulted in a better clinical response, associated to a better LVEF [4].

A long-term experiment using the intracoronary stem cell infusion in humans, from 2008 to 2010, was performed. The patients were divided in two groups: group I, composed by patients with Functional Class I and II, and group II, composed by patients with Functional Class II and III. After this procedure, the patients were evaluated through

echocardiographic exams and, accordingly the study, those patients who had an augment of LVEF more than 5% were considered as performing a good therapeutic response [7].

The results have shown that approximately 77% of these patients had good therapeutic response, the most of them classified as group 1. Besides, the percentage of survival rate after 5 years was 69%, and this therapy was considered a secure treatment because it did not show adverse effects [7].

Experiments in humans and animals are being performed, in order to proven the efficacy of this treatment, as how to show possible malefic effects. One of these experiments, performed in rats through the use of doxorubicin to induce dilated cardiomyopathy, was recently published. After this medication, the development of this pathology, through echocardiographic, electrocardiographic and usage of troponin I exams, was proven [2].

The animals were divided in two groups. The first group has received the infusion of enriched plaque plasma and the second one has received the infusion of mesenchymal stem cells. The analysis has evidenced that the group treated with enriched plaque plasma has shown an augment of inflammatory factors due to an increase of MCP-1 expression [2].

Morschbacher et al., (2016) [2], highlighting Nagaya et al., (2005) [3], have observed that the previously describe experiment has shown benefic effects regarding the cardiac functioning, related to stem cell use, probably due to the development of mechanisms that increase the angiogenesis and anti-apoptotic factors, like vascular endothelial growth factors and insulin-like growth factors.

Kelkar et al., (2015) [6], emphasizing Gnecci et al., (2008) [8], inform that this therapy promotes the progenitor endothelial cells migration to the target organ, and it is also involved with extracellular matrix regulation, allowing an augment in perfusion and improvement in myocardial function.

The research advancement in stem cell use was

Table 1. Studies with Stem Cells in dilated cardiomyopathy.

Autor(s)	Performed study	Period of study	Results	Results
Gárzon et al., 2016 [7]	Dilated idiopathic cardiomyopathy treated with intracoronary infusions of autologous cells of bone marrow	2008 to 2010	77% had an augment of \geq 5% in LVEF	The most common practices identified were homeopathy, Bach floral and oriental massage.
Morschbacher et al., 2016 [2]	Treatment of dilated cardiomyopathy (DMC) in rabbits with mesenchymal stem cells (MSC), transformed in enriched plaque plasma		The MSC transplant had diminished the DMC rate, improving the cardiac function, and also had demonstrated angiogenic factors production and reduction in apoptosis	Music, used as a facilitator of communication and movement, has been shown to attract the attention of the participants, placing it as a therapeutic option. It was shown able to facilitate the approach of people in the process of memory loss.
Haddad et al., 2015 [4]	Dilated long-term cardiomyopathy with 37 patients, LVEF < 40% and NYHA III submitted to intramyocardial injections of stem cells, tagged with Technecium-99m to evaluate its retention after 18 hours	2011 to 2012	Three months after SCT, there was a relative reduction of several cytokines and inflammatory markers	There is considerable evidence of efficacy for psychotherapeutic therapies in the treatment of coronary artery disease, headaches, insomnia, urinary incontinence, low back pain.
Gong et al., 2015 [9]	Use of stem cells collected from umbilical cord of humans to treat cardiomyopathy in transgenic rats		A month after the injection there was improvement of myocardial fibrosis, LVEF and diminishment of cardiac chambers.	This research suggests that meditation improves memory and reduces Alzheimer's risk by improving sleep, decreasing depression, increasing well-being and decreasing inflammatory regulatory genes. It also improves a number of aspects of mental health, all of which are important for maintaining cognitive function, thus reducing the multiple risks of Alzheimer's.

Source: Author's ownership.

innovated with a study performed in transgenic rats. Their cardiac function was altered, and the use of stem cells collected from human umbilical cord was tested. The results have shown great vantages compared to the use of stem cells collected from other human body structures, like bones [9].

The UCB-MSC (Umbilical Cord Blood Mesenchymal Stem Cells) use has demonstrated a significant improvement of cardiac function after the intramyocardial transplant in DCM rats, and this effect can be associated with reduction in cellular apoptosis,

inflammation, hypertrophy and fibrosis of myocardium. In a period of a month, there was improvement of cardiac function with amelioration of ejection fraction, reduction of myocardial fibrosis and reduction of heart chambers size [9].

Gong et al., (2015) [9], citing Jin et al., (2013) [10], highlight that, compared to other stem cells, those cells collected from umbilical cord have great potential of cellular differentiation, they are easily collected and, finally, they have a low immunogenicity; thus, they can be extremely adequate to

transplant, demonstrating greater possibility to be implemented in xenogenic tissues.

Despite the promising studies with stem cells in dilated cardiomyopathy, more experiments are necessary to better define this therapy as an effective treatment, better knowing its benefic and malefic effects.

References

1. Joanne P, Kitsara M, Boitard SE et al. Nanofibrous clinical-grade collagen scaffolds seeded with human cardiomyocytes induces cardiac remodeling in dilated cardiomyopathy. *Biomaterials*. 2015; 80 : 157-168.
2. Morschbacher P.D., Garcez T.N.A. , Paz A.H., Magrisso A.B., Mello H.F., Rolim V.M., Neuwald E.B., Driemeier D., Contesini E.A., Cirne-Lima E. Treatment of dilated cardiomyopathy in rabbits with mesenchymal stem cell transplantation and platelet-rich plasma. *Journal The Veterinary Journal* 209 (2016) 180-185.
3. Nagaya N., Kangawa K., Itoh T., Iwase T., Murakami S., Miyahara Y., Fujii T., Uematsu M., Ohgushi H., Yamagishi M., et al., 2005. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. *Circulation* 112, 1128-1135.
4. Hadad F, Sever M, Poglajen G, Lezaic L, Yang P, Maecker H, et al. Immunologic Network and Response to Intramyocardial CD34D Stem Cell Therapy in Patients With Dilated Cardiomyopathy. *J of Cardiac Failure* 2015; 21: 572-582.
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. American College of Cardiology Foundation, American Heart Association. 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the international society for heart and lung transplantation. *J Am Coll Cardiol* 2009; 53:e1e90.
6. Kelkar AA, Butler J, Schelbert EB, Greene SJ, Quyyumi AA, Bonow RO, et al. Mechanisms Contributing to the Progression of Ischemic and Nonischemic Dilated Cardiomyopathy Possible Modulating Effects of Paracrine Activities of Stem Cells. *J Am Coll Cardiol* 2015; 66:2038-47
7. Garzón F. B., Romero M., Lezo J.S., Pineda S.O., Herrera C., Lezo J.S. Miocardiopatía dilatada idiopática tratada con infusión intracoronaria de células autólogas de médula ósea: seguimiento a largo plazo. *Cartas científicas / Rev Esp Cardiol*. 2015; 68(8):719-730726.
8. Gnechchi M, Zhang Z, Ni A, et al. Paracrine mechanisms in adult stem cell signaling and therapy. *Circ Res* 2008; 103:1204-19.
9. Gong X, Wang P, Wu Q, Wang S, Yu L, Wang G. Human umbilical cord blood derived mesenchymal stem cells improve cardiac function in cTnTR141W transgenic mouse of dilated cardiomyopathy. *European Journal of Cell Biology* 2015.
10. Jin, H.J., Bae, Y.K., Kim, M., Kwon, S.J., Jeon, H.B., Choi, S.J., Kim, S.W., Yang, Y.S., Oh, W., Chang, J.W., 2013. Comparative analysis of human mesenchymal stem cells from bone marrow, adipose tissue, and umbilical cord blood as sources of cell therapy. *Int. J. Mol. Sci.* 14, 17986-18001.

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