Editorial

Stem Cell Therapy. A New Perspective for the Treatment of Ischemic Heart Failure

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Millions of people throughout the world have chronic heart failure, with ischemia being one of its most prevalent causes. It is a serious public health problem. The current treatments complementary to the optimized clinical treatment, such as cardiomyoplasty, heart transplantation, and different types of pacemakers, along with mechanical devices of ventricular support have not been established as standard procedures. Each of them has its own disadvantages, creating a field for study and application of alternative techniques. Of the latter, transplantation of exogenous stem cells to the impaired myocardium, aiming at improving cardiac performance, a process called cell cardiomyoplasty, seems to have a promising future [1-3].

Stem cells constitute a population of immature tissue precursor cells capable of self-renewal and production or replacement of cells of many tissues [4]. Different methods of treatment with stem cells have already been or continue to be used, although still in an initial phase of clinical application; a better assessment of the real applicability of stem cells, however, requires long-term results.

Currently, the 2 existing types of stem cell therapy aiming at regenerating cardiac muscle or improving its vascularization are as follows: 1) use of embryonic stem cells [5]; and 2) use of adult somatic stem cells [6].

The embryonic stem cells derived from the blastocyst are pluripotent, ie, they have the capacity to differentiate into over 200 types of tissue cells that exist in the human body. The somatic stem cells of adults, which were believed to have only a restricted action, may also exhibit a certain degree of pluripotency; bone marrow stem cells have been used for repairing other tissues, such as skeletal muscle, cerebral tissue, and hepatocytes [7,8].

Although embryonic stem cells have a greater potency to differentiate into cardiomyocytes, their use has been restricted to the experimental field in animals because of the inherent immunogenic component, in addition to their greater tendency towards causing arrhythmias and generating tumors, and obviously, the ethical conflicts triggered by them [7]. In an attempt to overcome these difficulties, the use of somatic stem cells of the adult himself, such as cardiac stem cells, muscle stem cells (satellite cells or skeletal myoblasts), and bone marrow stem cells, has increased. The latter have predominated in the most recent experimental and clinical studies. Honold et al. [9] provide an updated review on the subject.

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The way bone marrow stem cells are transplanted or mobilized to the impaired cardiac tissue varies as follows: peripheral intravenous instillation; intramyocardial injection (epicardial or endocardial); intracoronary injection; and, finally, the use of cytokines that stimulate the bone marrow [10]. Each of those methods has its disadvantages. Intravenous instillation is the least effective, because coronary output is a small part of the systemic output, and, therefore, a large series of cycles would be required so that the amount of stem cells in the impaired myocardial area could be appropriate, in addition to the great chance of cell deposition in organs other than the heart. Regarding the intramyocardial injections in the borders of the infarcted areas, through both the endocardial and epicardial routes, no general consensus exists that the injected cells are capable of migrating and substantially repairing the impaired myocardium. That which has been observed in some small experimental animals may not be extrapolated to human beings, considering that the impaired areas are substantially greater. In addition, that route by itself may lead to myocardial lesion or induce arrhythmias. The intracoronary route seems to be the most effective and least harmful, because the cells injected are selectively directed to the impaired area and no inconvenience resulting from the production of a myocardial lesion or induction of arrhythmia exists [10].

Recently, Murad-Netto et al. [11] carried out a non-randomized study of 14 patients with severe ischemic cardiomyopathy, who underwent autologous transendocardial transplantation of bone marrow mononuclear cells. Those authors reported an improvement in the patients' symptoms and in their exercise capacity until the sixth month after transplantation when compared with the evolution of 7 controls. The results obtained in that same group of patients until the fourth month of evolution have also been published[12]. After 6 months of evolution, the assessment of the 13 patients treated (one patient died suddenly in the 14th week of follow-up) revealed an improvement in functional class and a reduction in the anginal symptoms as compared with that of the 6 controls (one control died in the second week of follow-up). Neither an improvement in the ejection fraction nor a significant alteration in the cavitary volumes occurred in the group studied. Oxygen consumption and the size of the ischemic area showed only a marginal improvement between the groups in the sixth month of evolution. It is worth emphasizing that in a previous publication [12] with data of 2 and 4 months of evolution, both an improvement in the ejection fraction and a reduction in the left ventricular end-systolic volume were observed, indicating data loss throughout evolution.

The literature available shows the existence of some other

centers with initial experience in the subject. For analytical purposes, the access route of cell implantation should be considered, because, in clinical practice, both the open epicardial approach, complementing the procedures of surgical revascularization, and the endocardial and intracoronary approaches, in the hemodynamic laboratory, have been used.

Among those using the transepicardial approach, Ozbaran et al. [13] reported the evolution of 6 patients diagnosed with ischemic cardiomyopathy (LVEF=25%), who underwent myocardial cell transplantation of bone marrow stem cells and associated coronary artery bypass grafting. Those patients were followed up for up to 4 months and the authors reported a significant improvement in their quality of life expressed as an improvement in their functional class with marginal benefits in the echocardiographic data, in thallium scintigraphy, and in the positron emission tomography. Stamm et al. [14], with the same approach, followed up 12 patients and reported, with the aid of scintigraphy, a significant improvement in the perfusion area treated, a reduction in the left ventricular end-diastolic volume (LVEDV=140±38 mL vs. 124±30 mL; P=0.004), and an increase in the ejection fraction (39.7±9% vs. 48.7±6%; P=0.007). It is worth noting the occurrence of greater preoperative ejection fraction values when compared with those reported by Ozbaran et al. [13], who selected only those with an EF=25%. In the latter, the only marginal improvement may have resulted from the greater degree of fibrosis before the procedure.

Among those using the transendocardial route, Tse et al. [15] reported the experience with 8 patients with severe ischemic heart disease who underwent implantation of stem cells originating from the bone marrow, guided by the percutaneous procedure. After a 3-month follow-up, those authors reported, based on magnetic resonance imaging findings, an improvement in symptoms in addition to an improvement in myocardial perfusion and in the function of the area treated. On the other hand, Fuchs et al. [16] followed up 10 patients with coronary heart disease. After 3 months, those authors observed an improvement in the anginal scores. The exertion duration on exercise testing, assessed in 9 patients, was greater, although not significantly (391±155s vs. 485±198s; P=0.11). Perin et al. [17] reassessed their results at 6 and 12 months of evolution and observed that, at 12 months of evolution, the exercise capacity in the group treated was significantly better than that in controls. It is worth noting that they report the evolution of only 11 patients and not of the 14 patients in the original group. They may have assessed only the survivors, jeopardizing the appropriate interpretation of the results.

Regarding the evolution of patients undergoing stem cell transplantation through intracoronary route, Wollert et al. [18] used bone marrow cells in a randomized study with 30 patients and 30 controls with acute myocardial infarction undergoing primary or rescue angioplasty, who maintained a significant area of akinesia or hypokinesia after the procedure. After 5 to 6 months of evolution, the ejection fraction in the control and treated patient groups improved by 0.7±8.1% and 6.7±6.5%, respectively (P<0.01). No significant arrhythmias were observed during the evolution. Britten et al. [19] have also injected bone marrow stem cells in the culprit artery of 28 patients 4.7±1.7 days after acute myocardial infarction. The patients were reassessed after 4 months, and the following findings were observed: a significant increase in the ejection fraction (from 44±10% to 49±10%; P=0.003); a decrease in the end-systolic volume (from 69±26 to 60±28 mL; P=0.003); and no alteration in the end-diastolic volume (122±34 versus 117±37 mL; P=NS). Avilés et al. [20] studied 5 patients with acute myocardial infarction of the anterior wall who underwent fibrinolysis followed by angioplasty in the first 24 hours, and in whom a TIMI III flow was obtained without a significant residual obstruction. Approximately 10 to 15 days after those procedures, the patients received an infusion of bone marrow stem cells through the intracoronary route and were followed up for 6 months. No significant alteration was observed in the following parameters: end-diastolic volume; end-systolic volume; and ejection fraction.

In conclusion, the procedure, regardless the route used, bears an extremely low risk, and usually reduces the recurrence of symptoms. It also seems to reduce the ischemic area, although with no significant effect on cardiac volumes, and its effect on the ejection fraction is very variable. Obviously, the low number of patients studied, the lack of adequate control groups and of randomization, the non-uniform selection criteria of patients, and the bias caused by the concomitance of procedures, such as angioplasty and revascularization surgery should be seriously considered when assessing the results. In addition, the follow-up period was short, and all the studies available do not represent more than one year of evolution. Finally, as Al-Radi et al. [21] have already reported, the adequate amount of cells to be transplanted is yet to be defined, and occasional failures regarding hemodynamic improvement may be due to insufficient inoculations, and noxious effects may perhaps be avoided with a reduction in the amount of injected cells.

Although this is a promising technique, prospective, randomized studies with strict inclusion criteria and a long-term follow-up are required before it can be considered a therapeutic option for the treatment of ischemic heart disease.

References

1. Hughes S. Cardiac Stem Cells. J Pathol 2002; 197: 468-78.
2. Reffelmann T, Leor J, Muller-Ehmsen J et al. Cardiomyocyte transplantation into the failing heart - new therapeutic approach for heart failure? Heart Fail Rev 2003; 8: 201-11
3. Sim EK, Jiang S, Ye L, Lim YL, Ooi OC, Haider KH. Skeletal myoblast transplant in heart failure. J Card Surg 200; 18: 319-27.
4. Strauer BE, Kornowski R. Stem cell therapy in perspective. Circulation 2003; 107: 929-34.
5. Min JY, Yang Y, Converso KL et al. Transplantation of embryonic stem cells improves cardiac function in postinfarcted rats. J Appl Physiol 2002; 92: 288-96.
6. Yoon PD, Kao RL, Magovern GJ. Myocardial regeneration. Transplanting satellite cells into damaged myocardium. Tex Heart Inst J X1995; 22: 119-25.
7. Cardoso FP, González JH, Ezquerra EA. Stem cells to regenerate cardiac tissue in heart failure. Rev Esp Cardiol 2003; 56: 935-9.
8. Henningson CT Jr, Stanislaus MA, Gewirtz AM. Embryonic and adult stem cell therapy. J Allergy Clin Immunol 2003; 111(2 Suppl): S745-53.
9. Honold J, Assmus B, Lehman R, Zeiher AM, Dimmeler S. Stem cell therapy of cardiac disease: an update. Nephrol Dial Transplant 2004; 19: 1673-7.
10. Timmermans F, De Sutter J, Gillebert TC. Stem cells for the heart. Are we there yet? Cardiology 2003; 100: 176-85.
11. Murad-Netto S, Moura R, Romeo LJM et al. Terapia de células-tronco no infarto agudo do miocárdio, através de perfusão coronariana retrógrada. Uma nova técnica. Arq Bras Cardiol 2004; 83: 349-351.

12. Perin EC, Dohmann HF, Borojevic R et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 2003; 107: 2294-302.
13. Ozbaran M, Omay SB, Nalbantgil S et al. Autologous peripheral stem cell transplantation in patients with congestive heart failure due to ischemic heart disease. Eur J Cardiothorac Surg 2004; 25: 342-50.
14. Stamm C, Kleine HD, Westphal B et al. CABG and bone marrow stem cell transplantation after myocardial infarction. Thorac Cardiovasc Surg 2004; 52: 152-8.
15. Tse HF, Kwong YL, Chan JK, Lo G, Ho CL, Lau CP. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. Lancet 2003; 361: 47-9.
16. Fuchs S, Satler LF, Kornowski R et al. Catheter-based autologous bone marrow myocardial injection in no-option patients with advanced coronary artery disease: a feasibility study. J Am Coll Cardiol 2003; 41: 1721-4.
17. Perin EC, Dohmann FR, Borojevic R et al. Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. Circulation 2004; 110: II213-II218
18. Wollert KC, Meyer GP, Lotz J et al. Randomized controlled clinical trial of intracoronary autologous bone marrow cell transfer post myocardial infarction. Circulation 2003; 108: 2723.
19. Britten MB, Abolmaali ND, Assmus B et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging Circulation 2003; 108: 2212-8.
20. Avilés FF, San Roman JA, Frade JG et al. Intracoronary stem cell transplantation in acute myocardial infarction. Rev Esp Cardiol 2004; 57: 201-8.
21. Al-Radi OO, Rao V, Li RK, Yau T, Weisel RD. Cardiac cell transplantation: closer to bedside. Ann Thorac Surg 2003; 75: S674-7.