Cardiac Stem Cell Therapy: A Brief Review of Clinical and Experimental Studies

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Abstract

Myocardial regeneration utilizing novel cell-based therapies, gene transfer, and growth factors may prove to play an important role in the management of heart disease. Clinical trials have been published for a variety of biologics methods: systemic infusion, intracoronary infusion, trans venous coronary sinus, and intramyocardial. This review aims to address the recent aspects of the relationships between cardiac stem cell therapy and cardiovascular disease.

Keywords: Cell therapy, Regeneration, Cardiac remodeling

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world [1]. Despite recent advances in diagnostic, prevention and treatment of coronary heart disease (CHD) is still the leading cause of morbidity and mortality. Although current treatment options, such as diet, exercise, pharmacological therapies, stents *cardiac* pacing, resynchronization *therapy* and revascularization procedures have achieved important advances, these treatments are not always completely effective and do not restore permanently the function of myocardium.

Stem cells are undifferentiated biological cells that can differentiate into specialized cells and can divide to produce more stem cells. There are three known accessible sources of autologous adult stem cells in humans: (1) Bone marrow, which requires extraction by *harvesting*, that is, drilling into bone; (2) Adipose tissue (lipid cells), which requires extraction by liposuction; (3) Blood, which requires extraction through apheresis, where in blood is drawn from the donor, and passed through a machine that extracts the stem cells and returns other portions of the blood to the donor.

The four major techniques for stem cell administration that will be addressed include: (1) intramyocardial which include epicardial and transendocardial; (2) intracoronary; (3) trans venous coronary sinus; and (4) intravenous [2-11].

We searched Embase, Scielo, Europubmed, Cochrane, PubMed and CINAH databases (2003 to November 2015), using the following search strategy: ("autologous bone marrow cells" or "stem cells" or "cardiac cell" or "progenitor cell") and ("acute myocardial infarction" or "coronary artery disease" or "cardiomyopathy" or "heart failure"), systematic review, meta-analysis**,** clinical trials, and randomized. We will discuss results below on select clinical and experimental trials.

A total of 107 citations were screened, yielding eventually 16 clinical studies and 5 on experimental studies. Main reasons for exclusion were focus on, end-stage renal failure, pulmonary hypertension, or revascularization strategies and studies of low scientific quality.

Efficacy is an intrinsic property of a clinical course. Effectiveness is the result of the interaction of the treatment with the environment in which it is being applied. Both have demonstrated good results as described in the studies below.

Clinical studies

A meta-analysis of 33 trials studying transplantation of adult bone-marrow-derived

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Page 2 of 5

cells to improve cardiac function after myocardial infarction, led to significant improvement in left ventricular ejection fraction (LVEF). However, this improvement in ventricular function was not associated with significant improvements in morbidity or mortality [12].

In a REPAIR-AMI trial, autologous bone marrow cells led to improved outcomes and ventricular function in patients after myocardial infarction at 2 years. The recent clinical trials evaluating the safety and efficacy of bone-marrow-derived cell therapies have been somewhat discouraging [13].

The TIME trial did not show any improvement in ventricular function after intra- coronary delivery of autologous bone marrow cells. In the POSEIDON trial, not showed an improvement in global ventricular after transendocardial delivery of bone-marrow-derived cells in patients with ischemic cardiomyopathy [14].

The SCIPIO phase 1 trial demonstrated a 12.3% improvement in LVEF 1 year after intracoronary injection with autologous c-kit+, lineage- CPCs following myocardial infarction. The results of the SCIPIO trial indicate that intracoronary delivery of autologous c-kit+ CSCs leads to a significant clinical improvement in patients with ischemic cardiomyopathy, which is supported by improvement in LV systolic function and reduction in infarct size in the treated group [15]. In the CADUCEUS phase 1 trial, patients 2-4 weeks post myocardial infarction were randomized to receive an intracoronary injection of cardiosphere-derived autologous stem cells or standard of care. There was no significant difference between the two groups in measures of LVEF, there was a reduction of the scar mass and an increase of viable tissue and regional contractility when evaluated by cardiac magnetic resonance imaging at 6 months [16-18]. No adverse events were reported in either study at 6 months (CADUCEUS) or 1 year (SCIPIO).

In a study that enrolled 21 patients with dilated cardiomyopathy (DCM) (left ventricular ejection fraction [LVEF] <40%, who underwent peripheral stem cell mobilization. The majority of patients were mean age 53 ± 9 years, LVEF 25 ± 5%, and 6-minute walking distance 354 ± 71 m. Myocardial perfusion defects at rest were observed in 86% of patients and were more common in the left anterior descending territory (50%). At 6 months follow-up, there was a significant improvement in rest myocardial perfusion scores (6.3 ± 5.8 vs 3.1 ± 4.3; P <0.001), LVEF (25 ± 7% vs 29 ± 8%; P =0.005), and 6-minute walking distance (354 ± 71 m vs 404 ± 91 m; P <0.001). Stem cell therapy had lower summed rest perfusion score at both baseline (3.2 ± 3.0 vs 9.1 ± 6.3; P =0.015) and follow-up (1.0 ± 1.5 vs 5.0 ± 5.1; P =0.028). CD34 (+) cell transplantation may lead to improved myocardial perfusion in patients with DCM [19].

In another study the authors investigated whether discrepancies in trials of use of bone marrow stem cells in patients with heart disease account for the variation in reported effect size in improvement of left ventricular function. There were over 600 discrepancies in 133 reports from 49 trials. There was a significant association between the number of discrepancies and the reported increment in EF with bone marrow stem cell therapy (Spearman's r=0.4, P=0.005). Trials with no discrepancies were a small minority (five trials) and showed a mean EF effect size of -0.4%. The 24 trials with 1-10 discrepancies showed a mean

effect size of 2.1%. The 12 with 11-20 discrepancies showed a mean effect of size 3.0%. The three with 21-30 discrepancies showed a mean effect size of 5.7%. The high discrepancy group, comprising five trials with over 30 discrepancies each, showed a mean effect size of 7.7% [20].

In this meta-analysis to evaluate the efficacy of bone marrow-derived mononuclear cell (BMMNC) therapy in patients with AMI, the results of 22 randomized controlled trials (RCTs), LV ejection fraction increased by +2.10% (95% confidence interval [CI], 0.68-3.52; P=0.004) in the BMMNC group as compared with controls, evoked by a preservation of LV end-systolic volume (-4.05 mL; 95% CI, -6.91 to -1.18; P=0.006) and a reduction in infarct size (-2.69%; 95% CI, -4.83 to -0.56; P=0.01). There was no effect on cardiac function, volumes, or infarct size, when only RCTs (n=9) that used MRI-derived end points were analyzed. Intracoronary infusion of BMMNC does not enhance cardiac function on MRI-derived parameters, and improved clinical outcome [21].

In this systematic review an overview of preclinical and clinical studies performed on cell therapy for DCM, in total, 29 preclinical and 15 clinical studies were included. Stem cell therapy has shown moderate effects in clinical trials for ischemic heart disease [22].

The authors also performed a meta-analysis of 210 participants, the pooled analyses showed that cell therapy did not significantly improve LVEF compared with the control (95% CI -0.35 to 0.31, p=0.91). Nevertheless, cell therapy provided a benefit in increasing 6-minute walk distance (95% CI 21.09 m-142.62 m, p=0.008), improving MLHF score (95% CI -25.21 to -3.55, p=0.009), and lowering the incidence of NYHA functional class deterioration (95% CI 0.05-0.76, p=0.02). Intramyocardial cell therapy was feasible in treating patients with ischemic heart failure [23].

Another study with six patients were injected with autologous MSCs into akinetic/hypokinetic myocardial territories, MRI was used to measure scar, perfusion, wall thickness, and contractility at baseline, at 3, 6, and 18 months and to compare structural and functional recovery in regions that received MSC injections alone, revascularization alone, or neither. A composite score of MRI variables was used to assess concordance of antifibrotic effects, perfusion, and contraction at different regions. After 18 months, patients receiving MSCs exhibited increased LV ejection fraction (+9.4 ± 1.7%, P=0.0002) and decreased scar mass (-47.5 ± 8.1%; P<0.0001) compared with baseline. MSC-injected segments reduction in scar size, perfusion, and contractile improvement (concordant score: 2.93 ± 0.07), whereas revascularized (0.5 ± 0.21) and non treated segments (-0.07 ± 0.34) demonstrated non concordant changes (P<0.0001 versus injected segments). Intramyocardial injection of autologous MSCs into akinetic yet non revascularized segments produces comprehensive regional functional restitution, which in turn drives improvement in global LV function. These findings, although inconclusive because of lack of placebo group, have important therapeutic and mechanistic hypothesis [24].

In the PRECISE Trial, adipose-derived regenerative cells (ADRCs) can be isolated from liposuction aspirates and prepared as fresh cells for immediate administration in cell therapy. The authors conduced the first randomized, placebo-controlled, double-blind trial to examine the safety and feasibility of the

transendocardial injections of ADRCs in patients with ischemic cardiomyopathy. Procedural, postoperative, and follow-up safety end points were monitored up to 36 months. After baseline measurements, efficacy was assessed by echocardiography and single-photon emission computed tomography (6, 12, and 18 months), metabolic equivalents and maximal oxygen consumption (MVO2) (6 and 18 months), and cardiac magnetic resonance imaging (6 months). The authors enrolled 21 ADRC-treated and 6 control patients. Liposuction was well tolerated, ADRCs were successfully prepared, and transendocardial injections were feasible in all patients. No malignant arrhythmias were seen. Adverse events were similar between groups. Metabolic equivalents and MVO2 values were preserved over time in ADRC-treated patients but declined significantly in the control group. The difference in the change in MVO2 from baseline to 6 and 18 months was significantly better in ADRC-treated patients compared with controls. The ADRC-treated patients showed significant improvements in total left ventricular mass by magnetic resonance imaging and wall motion score index. Single-photon emission computed tomography results suggested a reduction in inducible ischemia in ADRC-treated patients up to 18 months. Our results suggest that ADRCs may preserve ventricular function, myocardial perfusion, and exercise capacity in these patients [25].

In a systematic review and meta-analysis of randomized controlled trials, 11 RCTs with 492 participants were included. The primary endpoint was change in left ventricular ejection fraction (LVEF). Secondary endpoints were changes in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). Intramyocardial BMC transplantation increased LVEF (4.91%; 95% confidence interval [CI] 2.84%-6.99%; $P < 0.00001$), reduced LVESV (10.66 mL; 95% CI, −18.92 mL to −2.41 mL; $P = 0.01$), and showed a trend toward decreased LVEDV (−7.82 mL; 95% CI, −16.36 mL–0.71 mL; $P = 0.07$). Patients suitable for revascularization with coronary artery bypass grafting had greater improvement in LVEF (7.60%; 95% CI, 4.74%-10.46%, $P < 0.00001$) than those unsuitable for revascularization (3.76%; 95% CI, 2.20%-5.32%; $P < 0.00001$). LVEDV reduction was also more significant in revascularizable IHD (−16.51 mL; 95% CI, −22.05 mL to −10.07 mL; $P < 0.00001$) than non-revascularizable IHD (−0.89 mL; 95% CI, −8.44 mL–6.66 mL; $P = 0.82$). Intramyocardial BMC injection improvement in left ventricular dysfunction and reduction in left ventricular volume in this study [26].

Experimental Studies

The authors also performed a systematic literature search to identify controlled preclinical trials of unmodified stem cell therapy in large animal models of myocardial ischemia. Data from 82 studies involving 1415 animals showed a significant improvement in mean left ventricular ejection fraction in treated compared with control animals (8.3%, 95% confidence interval, 7.1-9.5; P<0.001). Meta-regression revealed a similar difference in left ventricular ejection fraction in autologous (8.8%, 95% confidence interval, 7.3-10.3; n=981) and allogeneic (7.3%, 95% confidence interval, 4.4-10.2, n=331; P=0.3) cell therapies. Autologous and allogeneic cell therapy for ischemic heart disease show a similar improvement in left ventricular ejection fraction in large animal models of myocardial ischemia [27].

In an investigation of percutaneous intramyocardial injection of bone marrow mesenchymal stem cells (MSC) and autologous bone marrow-derived mononuclear cells (BMMNC) on cardiac functional improvement in porcine with acute myocardial infarcted (AMI) hearts. The authors induced an AMI in 22 minipigs. Two weeks post AMI, BMMNC (n = 7, 245 ± 98×10(6)), MSC (n = 8, 56 ± 17×10(6)), or phosphate buffered saline (PBS; n = 7) were injected intramyocardially. Cardiac function and myocardial perfusion were analyzed by echocardiography(ECHO) and gated single-photon emission computed tomography (SPECT) and computed tomography (CT) at 1 week before AMI and 2 and 10 weeks after AMI. Cell engraftment, proliferation, vascular density, and cardiac fibrosis were evaluated by histology analysis. In all groups, the ECHO revealed no significant change in the left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), or left ventricular end-diastolic volume (LVEDV), at 10 weeks after AMI compared with those at 2 weeks after AMI. The wall motion score index (WMSI) and left ventricular systolic wall thickening (WT%) were significantly improved at 10 weeks compared with those at 2 weeks after AMI in the MSC group (WMSI 1.55 ± 0.06 vs. 1.87 ± 0.10, WT 33.4 ± 2.3% vs.24.8 ± 2.7%,p < 0.05) but not in the BMMNC group. The myocardial perfusion quantified by SPECT/CT was improved in both the MSC and BMMNC groups, whereas the MSC group showed a superior improvement in vascular density and collagen volume fraction (p < 0.05). This suggests that when delivered by percutaneous intramyocardial injection, MSC might be more effective than BMMNC to improve ischemia and reperfusion after AMI [28].

Stem cell factor (SCF), a ligand of the c-kit receptor, is a critical cytokine, which contributes to cell migration, proliferation, and survival. It has been shown that SCF expression increases after myocardial infarction (MI) and may be involved in cardiac repair. The authors induced a transmural MI was created by implanting an embolic coil in the left anterior descending artery in Yorkshire pigs. The pigs received direct intramyocardial injections one week after the MI of either a recombinant adenovirus encoding for SCF(Ad. SCF, n=9) or β-gal (Ad.β-gal, n=6) into the infarct border area. At 3 months post-MI, EF increased by 12% relative to baseline after Ad. SCF therapy, whereas it decreased by 4.2% (P=0.004) in pigs treated with Ad.β-gal. Preload-recruitable stroke work was significantly higher in pigs after SCF treatment (Ad. SCF, 55.5 ± 11.6 mm Hg versus Ad.β-gal, 31.6 ± 12.6 mm Hg, P=0.005), indicating enhanced cardiac function. Histological analyses confirmed the recruitment of c-kit(+) cells as well as a reduced degree of apoptosis 1 week after Ad. SCF injection, and increased capillary density compared with pigs treated with Ad.β-gal was found at 3 months and suggests an angiogenic role of SCF. Local overexpression of SCF post-MI induces the recruitment of c-kit(+) cells at the infarct border area in AMI. SCF gene transfer in the chronic stages was associated with improved cardiac function in a preclinical model of ischemic cardiomyopathy [29].

In this study the authors aimed to evaluate whether BM-derived mononuclear cell (MNC) implantation can influence the post-MI structural remodeling, contractility and Ca(2+)-handling proteins of the remote in rats. After 48 h of MI, saline or BM-MNC were injected. Six weeks later, MI scars were slightly smaller and thicker, and cardiac dilatation was just partially prevented. However, the cardiac performance under hemodynamic stress was totally preserved in the BM-MNC treated group, and associated

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Page 4 of 5

with normal contractility of remote myocardium as analyzed in vitro. The decreased protein expression of the sarcoplasmic reticulum Ca(2+)-ATPase and phosphorylated-phospholamban and overexpression of Na(+)/Ca(2+) exchanger, were prevented by BM-MNC, indicating preservation of the Ca(2+) handling. The pathological changes on remodeled remote tissue such as myocyte hypertrophy, interstitial fibrosis and capillary rarefaction were also improved by cell therapy. BM-MNC therapy was able to prevent cardiac structural and molecular remodeling after MI, avoiding pathological changes on Ca(2+)-handling proteins and preserving contractile behavior of the viable myocardium, which could be the major contributor to the improvements of global cardiac performance after cell transplantation despite that scar tissue still exists [30].

In this study the authors compare the effects of the transplanted cardiac stem cells (CSCs) and mesenchymal stem cells (MSCs) transplantation on the electrophysiological characteristics and ventricular fibrillation threshold (VFT) in rats with myocardial infarction was induced in 30 male Sprague-Dawley rats. Two weeks later, animals were randomized to receive $5 \times 10(6)$ CSCs labeled with PKH26 in PBS or $5 \times 10(6)$ MSCs labeled with PKH26 in phosphate buffer solution(PBS) or PBS alone injection into the infarcted anterior ventricular free wall. Six weeks after the injection, electrophysiological characteristics and VFT were measured. Labeled CSCs and MSCs were observed in 5 μm cryostat sections from each heart. Malignant ventricular arrhythmias were significantly (P = 0.0055) less inducible in the CSC group than the MSC group. The VFTs were improved in the CSC group compared with the MSC group. Labeled CSCs and MSCs were identified in the infarct zone and infarct marginal zone. LabeledCSCs expressed Connexin-43, von Willebrand factor, α-smooth muscle actin and α-sarcomericactin, while the Labeled MSCs expressed von Willebrand factor, α-smooth muscle actin and α-sarcomeric actin in vivo. After 6 weeks of cell transplantation, CSCs are superior to MSCs in modulating the electrophysiological abnormality and improving the VFT in rats with MI. CSCs and MSCs express markers that suggest muscle, endothelium and vascular smooth muscle phenotypes in vivo, but MSCs rarely express Connexin-43 [31].

Limitations of study

The limitations of the study are inherent in the search for articles in languages other than English, and the inclusion of studies not yet published in peer-reviewed journals, which were only presented at congresses.

In conclusion, to date, no single cell type has proven itself to meet sufficient criteria for widespread use in clinical applications. These results are important for the design of future clinical trials. We need further extensive efforts to increase the efficacy of currently available methods, pre-clinical experiments using new techniques. Further studies will need to evaluate the potential therapeutic interventions with stem cells in cardiovascular disease.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Page 5 of 5

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