REVIEWS

The Use of Stem Cells in Cardiac Pathologies: A Review

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Despite the use of pharmacological therapies, the morbidity and mortality of cardiac diseases remain high. This paper aims to review multiple promising therapies and highlight the innovative role that stem cells can play. Stem cells have been identified as a potential therapeutic alternative to current mainstay medical and surgical interventions for cardiac pathologies, as these cells possess multipotent capabilities that could aid in cardiac regeneration and remodeling without the detriment of scar tissue. Numerous studies have explored the preliminary safety and efficacy of stem cell treatments in cardiac diseases, specifically ischemic heart disease (IHD), congenital heart disease (CHD), and dilated cardiomyopathy (DCM). IHD studies utilized intracoronary and intramyocardial delivery of various stem cell types and found efficacy with intramyocardial delivery of autologous mesenchymal stem cells injected into infarcted cardiac tissue. Similarly, CHD studies utilized intracoronary delivery of cardiosphere-derived cells in conjunction with the well-established Norwood Procedure and found benefits in cardiac function and somatic cell growth. DCM studies in murine models and subsequent clinical trials showed that transplantation with CD34+ stem cells, a cell type marked by muscle satellite cells, improved cardiac function and increased exercise capacity when delivered via intracoronary or transendocardial transplantation methods. While these cumulative results show promise, longer follow-ups and larger sample sizes are needed to validate the efficacy of this therapeutic approach for cardiac diseases in the long term. Stem cells, when combined with existing therapies, have the potential to mitigate the grave morbidity and mortality associated with cardiac pathologies.

Introduction

Despite the availability of pharmacologic therapies for cardiac diseases both in the US and globally, morbidity and mortality from this class of pathologies are still highly prevalent, with coronary heart disease as the leading cause (41.2%) of deaths attributable to cardiovascular disease, followed by stroke (17.3%), other cardiovascular diseases (16.8%), hypertension (12.9%), heart failure (9.2%), and disease pathology involving the arteries (2.6%).[1] This points to the need to look for other therapeutic options. Given this unmet need with present pharmacologic methods, stem cell therapy has been explored in recent years as a potential treatment for numerous diseases. Stem cells are defined as multipotent cells, which are able to develop into any end-organ tissue cells, renew themselves, and reside inside the body without eliciting an immune response (immunoprivileged).[2,3] In cardiac diseases specifically, many studies have explored the use of numerous stem cell types in ischemic heart disease (IHD), congenital heart disease (CHD), and dilated cardiomyopathy (DCM), where current treatment methods are either noncurative, costly, or limited in scope.[3]

The use of stem cells as therapeutics has spurred much debate, namely with regard to their source and uncertain long-term safety. Early research focused on human embryonic-derived stem cells before later pivoting to adult cell–derived stem cells. Given their unpredictability of differentiation and safety concerns,[4] adult cell–derived stem cells have become increasingly intriguing for use in human trials.[3] Many of these trials were conducted within the past decade and speculation on the long-term effects and limitations of their theses will be addressed. This review seeks to comprehensively explore the work to date involving adult stem cell use for the treatment of these cardiac pathologies.

Applications of Stem Cells in Cardiac Disease

Ischemic Heart Disease

IHD is the result of atherosclerosis progressively reducing coronary flow and thus oxygenation of cardiac tissue, causing left ventricular cell death and dysfunction.[5] The regenerative properties of stem cells have been harnessed as potential IHD therapies given that current treatments simply manage symptoms without repairing damage to the heart.[5] Historically, methods to deliver stem cells to the heart primarily include intracoronary or intramyocardial routes.

Intracoronary Infusion of Stem Cells

Infusion of an autologous stem cell solution into coronary vessels was one of the earliest methods of stem cell delivery explored in IHD as it was hypothesized to maximize benefit due to preexisting coronary catheterization methodology that created a minimally invasive and targeted delivery system.[6] Ischemic heart tissue releases inflammatory signals, such as stromal cell–derived factor 1 and vascular endothelial growth factor, that are involved in the process of stem cell homing.[7] These inflammatory cytokines play roles in signaling cascades that recruit intracoronary infused stem cells to the area to regenerate tissue.[6] Despite the early use of stem cell infusion, more recent trials exploring this delivery method have shown more mixed results. In the BOOST-2 (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial, intracoronary injection of bone marrow stem cells (BMSCs) failed to demonstrate ventricular improvement via improved left ventricular ejection fraction percentage increase compared with standard reperfusion therapy over a 6-month evaluation period in patients given low-dose BMSCs (n = 38; 95% CI, -3.0 to 4.1; $P = .76$) and high-dose BMSCs (n = 33; 95% CI, -2.6 to 4.7; $P = .57$), with the exception of patient groups with lower microvascular obstructions.[8]

Meanwhile, progenitor cells, which have more specified fates, have been harnessed to regenerate either the endothelial cells of blood vessels or cardiac muscle.

In porcine models, studies showed less promising results with intracoronary infusion of cardiomyocyte progenitor cells, with no difference from placebo in left ventricular ejection fraction (LVEF), left ventricular end diastolic and systolic volumes, and size of infarction (n = 16; $P = .34$, $P = .40$, and $P = .27$, respectively).[9] However, human trials have seen greater success. Intracoronary infusion of autologous bone marrow–derived circulating progenitor cells (capable of differentiating into endothelial cells) demonstrated a significant decrease in infarction size by 9% (n = 38; $P < .001$) and improved ejection fraction by 6% ($P = .02$) in patients with IHD over their baseline values over 12 months post procedure.[10] Further, more recent trials demonstrated a more than 10% improvement in ejection fraction 12 months after intracoronary injection of autologous progenitor cells in patients with ST-elevation myocardial infarction and 1-vessel coronary artery disease (n = 15; $P < .05$).[11]

Despite some promising results, intracoronary delivery relies on healthy vasculature to transmit chemical signals to guide stem cells toward damaged tissue, limiting efficacy in patient populations, such as those with advanced coronary artery disease, and perhaps making this method more suitable for acute events, such as acute myocardial infarction.[3,6] While more work may be required to demonstrate the benefit of cardiomyocyte progenitors in humans, the significant improvement in both cardiac function and functional status seen in human patients receiving bone marrow–derived progenitor cells signals a promising approach for future studies.

Intramyocardial Injection

Intramyocardial injection via catheterization, however, provides a more direct approach for chronic pathologies by delivering stem cells directly to an infarcted area, where damage signaling may be more limited.[3] Prior work has demonstrated better outcomes (measured by LVEF) with intramyocardial injection of BMSCs as compared with intracoronary injection (absolute difference, 3.60%, $P = .15$).[12] It is critical to note, as the authors did in their discussion, that the limited sample size (n =105) of the study does not definitively prove superiority of the intramyocardial method over intracoronary delivery. Nonetheless, numerous studies have explored the use of the more direct stem cell delivery method using either autologous stem cells (extracted from the same patient in a prior procedure) or other stem cell types intramyocardially injected into an infarcted area or its perimeter.[13-15]

Particularly, autologous mesenchymal stem cells (MSCs also referred as BMSCs; harvested from the patient's own bone marrow) seem to have demonstrated more consistent positive results over other types of stem cells in cardiac pathologies, such as ischemic heart failure, as demonstrated by the previously mentioned studies.[14,15] Catheterized injection of autologous MSCs was shown to improve LVEF, stroke volume, and myocardial mass over placebo (n = 55; $P < .001$ for all) in patients with untreatable severe ischemic heart failure.[13] Meanwhile, other studies did not show benefit in LVEF (n = 15; P

> .05) but still demonstrated positive symptomatic outcomes, such as timed walk distance at 6 months (95% CI, 10.8 to 45.5 m; *P* = .005) and Minnesota Living with Heart Failure Questionnaire score at 5 months (95% CI, −23.7 to 0.5; *P* = .006) when transendocardially injecting autologous MSCs.[16,17] To improve expansion yield, one study harnessed adipose-derived stromal cells expanded ex vivo for intramyocardial injection, leading to less of a decrease in exercise capacity (n = 40; mean (SD), 81 (6) W to 78 (10) W; *P* = .12) compared with placebo (n = 20; from a mean (SD) of 87 (12) W to 80 (12) W; *P* = .02) in patients with chronic IHD only after a 3-year follow-up.[5] All aforementioned studies recruited fewer than 70 participants, limiting their extrapolative value. However, the positive results seen with both functional and symptomatic markers in the studies highlight the value of using autologous MSCs in potential IHD therapies.

In contrast, studies using other autologous cell types demonstrated more neutral results, albeit with shorter time to follow-up. Intramyocardial injection of both autologous cardiopoietic cells and bone marrow CD133+ progenitor cells did not significantly improve nor reduce symptomatic end points in patients with left ventricular dysfunction (n = 102; *P* = .73); however, follow-ups were conducted at only 39 weeks after injection of cardiopoietic cells and at 6 months with use of CD133+ cells.[14] Similar results were seen in the study by Bartunek et al,[15] with no difference between CD133+ (n = 26) and placebo (n = 22) (mean (SD), 31% [7%] vs 33 [8%]; *P* = 0.3). Given positive outcomes can take as long as 3 years to develop with mesenchymal stem cells, longer times to follow-up may yield more promising results with progenitor cell types as well.[5]

Other Stem Cell Types

Novel cell types or sources have been evaluated for intramyocardial delivery in patients with IHD, including allogeneic mesenchymal stem or progenitor cells and aldehyde dehydrogenase–bright cells (a marker in primitive stem and progenitor cells isolated from bone marrow and peripheral blood denoting cells with strong hematopoietic and angiogenic potential).[16,18,19] Although allogenic stem cells were found to be safe without increased risk of adverse immune or cardiac events compared with autologous controls (n =15; *P* = .46 vs *P* = .12), they did not demonstrate benefit in quality-of-life end points such as 6-minute walk test (*P* = .31) and the Minnesota Living with Heart Failure Questionnaire (*P* = .34) over a 12-month period.[16,18] Similarly, aldehyde dehydrogenase–bright cells were found to be safe in patients with ischemic heart failure, but the novelty of the cell type invites further studies to augment the demonstration of its early safety with evidence of positive efficacy.[19]

Controversy in Stem Cell Use for Ischemic Heart Disease

One topic of controversy surrounding the clinical use of stem cells in IHD is their potential to cause arrhythmias. While severely understudied, the plausible mechanism behind the theory speculates a possible propensity of forming reentry circuits due to increasing amounts of tissue heterogeneity within areas

of cardiac ischemia injected with MSCs.[2,20] The newly injected MSCs would theoretically be unable to perform electric coupling, creating a greater risk for future arrhythmias during the period of cell regeneration. However, a post hoc analysis of the POSEIDON (A Phase I/II, Randomized Pilot Study of the Comparative Safety and Efficacy of Transendocardial Injection of Autologous Mesenchymal Stem Cells Versus Allogeneic Mesenchymal Stem Cells in Patients With Chronic Ischemic Left Ventricular Dysfunction Secondary to Myocardial Infarction) trial particularly studied the adverse effects of injected MSCs in the border zones of infarcted myocardium in patients with ischemic cardiomyopathy and concluded there were no proarrhythmic or dysrhythmic tendencies in patient groups injected with MSCs (n = 48; $P = .25$).[20] These findings are consistent with several other studies testing the use of stem cells in post–ST-elevation myocardial infarction therapy who also found no adverse effects of injection of MSCs, including the BOOST-2 trial.[8] Although the trial suggested there is no adverse arrhythmogenic effect when using intracoronary injection MSCs in the heart, it also concluded there is little to no benefit in using MSCs in patients with ischemic cardiac disease compared with current reperfusion and drug therapies.[8]

The POSEIDON study also examined a small subgroup of patients with low ventricular ectopy burden, in which MSC intracoronary injection showed a protective antiarrhythmic effect over short-term (several days) and long-term (1 year) evaluation compared with patient groups injected with placebo ($P = .001$ compared with $P = .07$).[20] Although these results seem promising, no other evidence or conclusive studies to date support this claim. Because this study was one of the first of its kind, its results warrant further clinical trials before translation into common clinical practice.

Given that the direct delivery of intramyocardial administration has seen positive symptomatic and/or functional outcomes, even in comparative studies, this approach appears to have great potential therapeutic value for patients with IHD with limited treatment options.[5,12-15] Many of these positive studies have harnessed autologous MSCs, with limited evidence to suggest arrhythmogenic potential. Further work must be done with longer follow-up times to evaluate long-term safety and efficacy of their use, as well as potential impact on mortality rates in recipients. However, evidence to date suggests intramyocardially injected MSCs have the capacity to safely improve functional and symptomatic outcomes in patients with IHD, justifying future studies in this approach.

Congenital Heart Disease

CHDs are a spectrum of diseases defined as structural abnormalities in the heart present at the time of birth and can be asymptomatic or cause symptoms such as arrhythmias, cyanosis, shortness of breath, fatigue, and edema.[21] CHDs are the most common birth defect and include incomplete or incorrect formation of heart chambers and vessels.[21] The ultimate complication of these

conditions is heart failure.[22] As it stands, surgical interventions and heart transplants are the standard treatment options for CHD.[21] However, both "solutions" are temporary and come with severe adverse effects and potential complications.[21]

On the other hand, stem cells are more easily obtained compared with transplant-eligible hearts and come with fewer potential risks.[21] Currently, stem cell therapies for CHD are predominantly in the preclinical stages of testing where they are being used both as models for CHD phenotypes and as therapies for CHD animal models. A limited number of clinical trials involving stem cells do exist for CHDs, predominantly addressing hypoplastic left heart syndrome (HLHS). HLHS is a subgroup of CHD and is characterized by the congenital underdevelopment of the left heart, which can cause reduced flow to the left ventricle and outflow through the aorta.[23] If left untreated, HLHS can cause left-sided heart failure, leading to cardiogenic shock and ultimately death.[23] The current management options for HLHS are heart transplant and/or a series of surgical procedures known as the Norwood procedure.[22] This procedure is composed of 3 surgical procedures that rebuild the aorta so that it can properly regulate blood circulation and is associated with a 5-year survival rate of 70% to 75%.[22] While the Norwood procedure remarkably improves morbidity, a number of clinical trials are using stem cell therapies as an adjunct to these surgical procedures in an effort to improve the long-term survival of patients with HLHS. It is worth noting that these trials have small sample sizes, ranging from 3 to 40, likely due to the low prevalence of HLHS of 0.001%.

A first prospective phase 1 clinical study by Ishigami et al[23] evaluated the feasibility of autologous cardiosphere-derived cells (CDCs) intracoronarily delivered after stages 2 and 3 of the Norwood procedure. At 18 months, CDC-treated patients demonstrated a higher right ventricular ejection fraction (n = 7; mean (SD), 31.5% [6.8%] vs 40.4% [7.6%]; $P = .049$), improved somatic growth ($P = .0005$), and reduced heart failure status ($P = .003$) as compared with the control group.[23] While this study demonstrated the feasibility of intracoronary CDC infusion in patients with HLHS, the potential effects needed to be further assessed. Thus, the same research team followed up the study with a randomized phase 2 trial.[24] This study showed that patients treated with CDCs had improved ventricular function (n = 17; 38.8% vs 34.8%; $P < .001$) compared with that of baseline in 17 controls post-CDC infusion. At the 1-year mark, palliative CDC infusion was associated with improved ventricular function (41.4% vs 35.0%; $P < .001$) and volumes ($P < .001$), a reduction in status of heart failure ($P < .001$), and somatic growth ($P < .001$) relative to baseline.[24] Results at both 3 months and 1 year after palliative infusion demonstrated reverse remodeling of damaged ventricle tissue. While these results are noteworthy, some limitations of this trial were the narrow range of patients with single ventricle physiology, the limited sample size, the inability for placebo infusion in children, and the lack of control group data.

Ultimately, stem cell and surgical interventions for HLHS may provide some benefits to cardiac function, somatic growth, morbidity rates, and quality of life.

The limitations of surgical palliation and the extensive waitlists for heart transplants create a gap in therapeutic care and thus lead to a high mortality rate for patients with CHD. The efficacy of stem cells enhances myocardiocyte regeneration, removes the need for immunosuppression, and decreases the chance of rejection. These benefits lend themselves to a therapy that would provide patients with decreased long-term risk. While clinical studies have not yet been conducted for other CHDs, the pathology of HLHS is a valuable surrogate for the applicability of stem cells in CHDs because it encompasses a combination of multiple individual manifestations of CHD; thus, success in HLHS treatment lends promise to stem cell therapies having broader applications in CHD treatment.

Dilated Cardiomyopathy

DCM is characterized by ventricular dilatation and systolic dysfunction and can present with symptoms such as fatigue, shortness of breath, and palpitations.[25] Of note, nonischemic DCM is one of the most common causes of advanced heart failure; however, DCM is still associated with a significant mortality rate, even with multiple available medical therapies such as spironolactone, beta-blockers, and angiotensin-converting enzyme inhibitors.[25] This trend points to the gap in available and effective therapeutic options that can significantly improve quality of life, morbidity, and mortality in patients with DCM.

One approach to addressing this therapeutic gap has been to leverage CD34+ cells to improve cardiac perfusion. CD34+ cells are a primitive bone marrow–derived multipotent hematopoietic stem and progenitor cell.[26] Within the last decade, stem cells, such as CD34+ cells, have made their debut in clinical research because these cells mobilize from the bone marrow and migrate to sites of inflammation and ischemia, eventually contributing to angiogenesis and vasculogenesis.[26] For therapeutic use in DCM, CD34+ cells are collected from the bone marrow via apheresis and injected into an intracoronary, intramyocardial, or transendocardial solution and then perfused into the area of defective flow.[27] Quantitative assessments such as LVEF, myocardial perfusion scores, and N-terminal pro-B-type natriuretic peptide (NT-proBNP; a diagnostic and prognostic marker of heart failure), as well as functional assessments, such as the 6-minute walk test distance, are often used as end points in studies assessing CD34+ cell transplantation utility and efficacy in patients with DCM.

Intracoronary and Transendocardial CD34+ Stem Cell Transplantation

In one such study, intracoronary transplantation of CD34+ cells in patients with nonischemic DCM was investigated. CD34+ cells were injected into the coronary artery supply that experienced reduced perfusion and increased myocardial dysfunction.[28] At 6 months, patients with DCM who underwent CD34+ stem cell intracoronary transplantation displayed significant improvement in LVEF (n = 21; 25% vs 29%; $P = .005$), myocardial perfusion scores (6.3 vs 3.1; $P < .001$), and 6-minute walk distance (354 m vs 404 m; $P < .001$). These results indicate the viability of CD34+ stem cell intracoronary transplantation in patients with nonischemic DCM. Another study examined transendocardial cell transplantation as a route of administration in patients with DCM. At 6-month follow-up, patients who underwent transendocardial transplantation showed improvement in LVEF (n = 31; 27.1% to 344.9%; $P = .001$), an increase in 6-minute walk distance (411 m to 496 m; $P = .001$), and a decrease in NT-proBNP level (3672 pg/mL to 1488 pg/mL; $P = .04$).[29] These results suggest that transendocardial CD34+ cell transplantation may be associated with improved exercise capacity and cardiac function. Interestingly, better clinical response to the stem cell therapy was particularly highlighted in patients who received higher doses of CD34+ cell therapy. The positive outcomes, yet short-term follow-up, of these studies merit further investigation through additional studies and longer-term follow-up with these patients.

Intracoronary vs Transendocardial CD34+ Stem Cell Transplantation

An investigative comparison of intracoronary and transendocardial CD34+ transplantations demonstrated that in patients with nonischemic DCM, transendocardial CD34+ cell transplantation is superior to intracoronary transplantation as demonstrated by improvement in LVEF, NT-proBNP, and functional assessments such as the 6-minute walk test distance ($P = .03$, $P = .03$, and $P = .04$, respectively).[27] These results point to transendocardial transplantation as the preferred method, leading to higher myocardial retention rates. However, there appears to be disharmony between the magnitude of increase in myocardial retention rates with the improvement in clinical parameters mentioned above. Furthermore, transendocardial CD34+ cell therapy in patients with refractory angina is not accompanied by an expected improvement in clinical outcome. These findings suggest that there are factors other than the increase in myocardial retention rates that contribute to improved clinical outcomes in patients receiving CD34+ cell therapy that may be investigated in future studies.

Right Ventricular CD34+ Stem Cell Transplantation

Right ventricular dysfunction also presents an important prognostic factor for nonischemic DCM. Frljak et al[30] showed that at 6 months, patients who received transendocardial cell therapy had a significant improvement in

echocardiographic parameters assessing right ventricular function such as LVEF (+6.9%; $P = .001$), laboratory tests such as NT-proBNP (-578 pg/mL; $P = .03$), and functional assessments such as the 6-minute walk test distance (+57 m; $P = .03$).[30] These findings also indicate the value of using CD34+ cell therapy in patients with right ventricular function impairment.

Single vs Multiple CD34+ Stem Cell Transplantation

Single-dose and repetitive administration of CD34+ cells have also been compared in patients with nonischemic DCM.[31] Patients in the repetitive cell therapy cohort repeated therapy at 6 months. Results of this study revealed that repetitive administration of transendocardial CD34+ cell transplantation did not seem to be associated with a significant improvement in LVEF ($P = .40$), NT-proBNP ($P = .33$), and 6-minute walk test ($P = .87$) when compared with a single-dose administration. One aspect to note, however, is that this study only followed up patients for 1 year, and results of cell therapy and its effects on these clinical parameters should be followed up in more long-term studies to determine the full efficacy of increased administration frequency of CD34+ stem cells in patients with DCM. Future follow-up studies should be conducted to reassess the clinical outcomes and determine the long-term safety and efficacy of stem cell use in patients with cardiac disease.

Conclusions

As the field of stem cell research continues to reach new milestones, the question of their utilization for highly prevalent cardiac diseases remains ever present. In particular, numerous permutations of studies have been conducted with stem cell therapy in the scope of IHDs, involving intracoronary or intramyocardial delivery, autologous or allogeneic stem cells, and stem or progenitor cells. Initial studies have suggested safety and limited efficacy with intramyocardial delivery of autologous mesenchymal stem cells injected into infarcted cardiac tissue; however, longer follow-up and greater sample sizes are needed to validate these initial results with such a novel therapeutic approach. As it currently stands, the true potential of such therapies remains unclear and complicated. It seems that in addition to dosage and the type of harvested stem cells, even the delivery methods and extent of comorbidities may impact their efficacy, which has yet to be assessed long-term. Perhaps more exclusion criteria limiting patient comorbidities, alignment on cell quality standards and delivery methods, and extended monitoring and follow-up may reveal their true efficacy and safety in future trials.

Additionally, studies have shown that there are clinical benefits to using intracoronary delivered cardiosphere-derived cells alongside palliative procedures in the treatment of CHDs, most notably in HLHS. The improved heart function seen in clinical trials shows promising trends to aid in the long-term survival of patients with HLHS in supplementation to the Norwood procedure, and advocates for more clinical research in other CHDs. Most importantly, these few studies proposed the efficacy of stem cells in

transplantation, which due to their immunoprivileged qualities may improve survival and adverse effects. However, little research has been done in CHDs outside of HLHS and the breadth of applicability to other CHDs must be further investigated.

Studies have also demonstrated improved cardiac function and increased exercise capacity in patients with DCM through the use of CD34+ stem cells. Whether the route of administration is intracoronary or transendocardial, multiple studies have shown improvement in LVEF and cardiac stress markers. Comparison between the two routes of administration have shown superiority for transendocardial over intracoronary transplantation and the efficacy of right ventricular CD34+ stem cell transplantation. However, many of these trials have yet to follow up with patients in the long-term, begging the question of whether this novel therapeutic approach in patients with DCM will have a lasting and even more pronounced beneficial effect. Of note, cardiac pathophysiology has improved but overall morbidity and mortality are still yet to be determined in patients receiving this therapy in the long run, which points to the need for additional research and long-term follow-up with patients currently enrolled.

Given all the studies discussed in this review, it seems safe to assume that stem cell research holds high potential in the development of treatments for cardiac disease that has yet to be completely fulfilled. Short-term safety and efficacy have been demonstrated in multiple studies. The fact that these studies have yet to disprove long-term adverse events or reactions is noteworthy; however, their auspicious results lead us to believe that they may likely become well-developed and notable cardiac therapies within the next decade. Moving forward, strict precautions should remain in place to protect patients until there is a broad base of long-term evidence around safety and efficacy. Increased efforts to further develop this field that address such a significant health problem are strongly encouraged and may have the capacity to define a new era in the realm of cardiac therapeutics.

Disclaimers

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