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STEM CELL THERAPIES IN PATIENTS WITH SINGLE VENTRICLE PHYSIOLOGY

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Abstract

Single ventricle physiology, especially hypoplastic left heart syndrome, is one of the most high-risk lesions in children with congenital heart disease, and the ensuing heart failure remains as a major problem related to adverse outcomes in these patients. The field of stem cell therapy for heart failure has shown striking advances during the past 10 years, and many clinical trials using stem cell technologies have been conducted in adults, which suggest that stem cell therapy is associated with long-term improvement in cardiac function. Cardiac progenitor cells have recently been discovered, and their strong regenerative ability has been demonstrated in several studies. Although no large clinical trials have been performed in the field of congenital heart disease, recent investigations indicate that stem cell therapy may hold great potential to treat children with cardiac defects.

Introduction

Single ventricle physiology encompasses a spectrum of rare and complex congenital heart defects characterized by the heart having only one functional pumping chamber to eject blood to the systemic and pulmonary circulation. Most patients require a series of staged surgical palliations including stage I palliation (systemic-pulmonary shunt or pulmonary artery banding) and Glenn (stage II) and Fontan (stage III) operations. Advances in surgical technique and postoperative management have dramatically improved the prognosis of young children and adolescents.[1] However, because of the palliative nature of the procedures, late hemodynamic complications including ventricular failure, atrial arrhythmias, protein-losing enteropathy, and thrombosis become increasingly frequent with age and are common in adulthood.[2, 3] Some of these patients will ultimately require heart transplantation for end-stage heart failure. Even after heart transplantation, a recent study showed that 5-year survival was 60% in patients who had undergone a Fontan operation.[4]

Among several risk factors related to adverse outcomes of these patients, such as elevated pulmonary artery pressure and atrioventricular valve insufficiency, impaired ventricular function is one of the major factors that affect the outcome.[5, 6] In particular, morphologic right ventricle is suboptimal for a systemic ventricle, as seen in congenital and surgically corrected transposition of the great arteries, and several outcome series have shown that patients with a dominant right ventricle have significant risk for heart failure accompanied by high mortality.[7-9] Analysis using speckle tracking imaging showed impaired systolic and diastolic functions in right ventricular morphology compared with those of the left.[10]

Although the mechanisms of ventricular dysfunction occurring in single ventricle physiology are not well understood, pathological studies have revealed interstitial fibrosis within the myocardium of patients with adult congenital heart disease, suggesting that myocardial fibrosis is a potential contributor.[11] Using cardiac magnetic resonance late gadolinium enhancement, a recent study has shown that 28% of patients who had undergone a Fontan operation presented with fibrosis in the ventricular myocardium. Patients with myocardial fibrosis had lower ejection fraction, increased end-diastolic volume, and higher frequency of ventricular tachycardia.[12] Another study using magnetic resonance imaging (MRI) showed that patients with adult congenital heart disease, particularly systemic right ventricle, had a larger quantity of diffuse fibrosis than normal controls.[13] Myocardial fibrosis in congenital heart disease was also associated with clinical symptoms, such as a higher New York Heart Association (NYHA) score and a decrease in exercise intolerance.[14] The fact that these findings were seen mainly in adult patients, most of whom had already completed staged surgical palliations, suggests that a surgical procedure cannot guarantee the full restoration of cardiac function. Thus, the development of additional therapy to improve cardiac function is extremely important for cardiac failure in patients with single ventricle physiology.

Stem Cell Therapy for Heart Failure in Children

A number of clinical trials with cell therapy have been carried out in adult patients with ischemic heart disease, and they demonstrated that transplantation of stem cells such as bone marrow cells improves left ventricle function, infarct size, and cardiac remodeling.[15] On the other hand, studies in children are limited to case reports (Table 1).

In 2009, Rupp et al. reported a case of cell therapy in an 11-month-old boy with hypoplastic left heart syndrome (HLHS).[16] The infant retained the status of chronic heart failure since he went through cardiogenic shock due to obstruction of ductus arteriosus after a hybrid stage I procedure that included bilateral pulmonary artery banding and ductal stenting. Even 7 months after a stage II procedure, he retained a status of NYHA class III heart failure with a dilated right ventricle and reduced ventricular function. The ejection fraction of the systemic right ventricle was 22% and brain natriuretic peptide (BNP) level was 2200 pg/mL. In this critical condition, autologous bone marrow cells (BMC) were

Target diseases	No. of patients	Age of patients	Follow-up (months)	Cell type	Delivery route	Outcome
HLHS (TICAP study)	14	5 mo – 3 y	12	CDC	IC	Improved RV systolic function
Single ventricle physiology (PERSEUS study)	34	0 – 20 y	12	CDC	IC	Currently recruiting patients
HLHS (Duke University)	20	0 – 2 d	12	UCB	IV	Currently recruiting patients
HLHS (Mayo Clinic)	10	0 – 18 mo	6	UCB	IM	Currently recruiting patients
HLHS[16]	1	11 mo	3	BMC	IC	RVEF increased 22%
DCM and CHD[17]	9	4 mo – 16 y	24 – 52	BMC	IC	NYHA and BNP decreased
DCM[18]	1	2 y	6	BMC	IC	LVEF increased 21% NYHA and BNP decreased
DCM[19]	2	6 y, 9 y	2 – 6	PSC	IC	LVEF increased 20% – 23% NYHA and BNP decreased
DCM[20]	1	4 mo	4	BMC	IM	LVEF increased 21%
DCM[21]	6	4 mo – 17 y	12	BMC	IM	LVEF increased 21%
Myocardial infarction[22]	1	9 y	3	BMC	IC	LVEF increased 22% NYHA score decreased

Table 1. Clinical trials and case reports of stem cell therapy in children with heart failure. HLHS: hypoplastic left heart syndrome; DCM: dilated cardiomyopathy; CHD: congenital heart disease; CDC: cardiosphere-derived cell; UCB: umbilical cord blood; BMC: bone marrow cell; PSC: peripheral stem cell; IC: intracoronary; IM: intramuscular; IV: intravenous.

given back to the patient by intracoronary bolus injection. One year after the cell therapy, his clinical condition had improved dramatically, his BNP level had decreased to 132 pg/mL, and his right ventricular ejection fraction had improved to 44%. The same group also reported two other cases of cell therapy using BMC for heart failure in children with congenital heart disease (double outlet right ventricle with pulmonary atresia and ventricular septal defect).[17] Although clinical presentation had improved in both patients, supportive data remained elusive.

Two clinical trials are underway using autologous umbilical cord blood cells for HLHS. A phase I study at Duke University is collecting and infusing the cells in newborn infants, and Mayo Clinic is planning a trial involving cell injections into the right ventricle of children undergoing a scheduled Glenn operation. The former study is also going to evaluate the improvement of neural injury in the treated infants.

As shown in Table 1, most of the cell therapies reported in children have targeted dilated cardiomyopathy. Among the studies in 4-month to 17-year-old children, left ventricular ejection fraction (LVEF) increased by roughly 20%, and clinical symptoms improved dramatically after the transplantation of BMC or peripheral stem cells.[18-21] Another group reported a case of BMC transplantation in a 9-year-old girl with congestive heart failure secondary to myocardial infarction (MI). After transcoronary infusion of BMC, LVEF improved from 30% to 47%.[22]

Although all studies to date are limited to case reports with small numbers of patients, the dramatic improvements shown in most of these studies lead to the assumption that children have a greater potential of heart regeneration and reactivity to cell therapy. To uncover the efficacy of cell therapy beyond its feasibility and safety, further study is necessary, including large-scale randomized clinical trials.

Cardiac Progenitor Cells

Although the mammalian heart has long been believed to be a terminally differentiated organ with no intrinsic capacity to regenerate after myocardial injury, recent identification of different classes of cardiac stem/progenitor cells has extensively challenged this dogma. In 2003, cardiac stem/progenitor cells expressing c-kit or Sca-1 were identified in adult mammalian heart; these were self-renewing, clonogenic, and multipotent, giving rise to myocytes, smooth muscle, and endothelial cells.[23-25] Later, another group reported that surgical or percutaneous endomyocardial biopsy specimens of human cardiac tissues grown in primary culture developed multicellular clusters called cardiospheres, which were plated to yield cardiosphere-derived cells (CDCs).[26, 27] CDCs do not require cell sorting by a cell surface marker using flow cytometry for isolation, and they show cardiogenic differentiation in vitro. In vivo, CDCs injected into the border zone of myocardial infarcts in mice promote regeneration of myocardium to achieve functional improvement of LVEF.

Biological mechanisms that contribute to the efficacy of cardiac cell therapy are not limited only to direct heart muscle and blood vessel regeneration from transplanted cells. The paracrine effect of tissue preservation, angiogenesis, and recruitment of endogenous repair is also one of the important mechanisms. Recent studies have demonstrated that CDCs secreted many growth factors, such as VEGF, HGF, and IGF-1, and have antiapoptotic effects on myocytes as well as proangiogenic effects on endothelial cells.[28] Among various stem cell types, CDCs exhibit a balanced profile of paracrine factor production and greatest myogenic differentiation potential in vitro. In vivo, CDCs provided superior improvement of cardiac function, the highest cell engraftment, and myogenic differentiation in experimental MI.[29]

Importantly, a recent study showed that infants have 4-fold more human CDCs than adults, and the cells exist mainly in the right atrium (RA) and the outflow tract.[30] Moreover, CDCs of infants have higher telomerase activity than those of adults. Another group has demonstrated that human CDCs isolated from neonates showed strong regenerative ability both in vitro and in vivo compared with adult-derived CDCs.[31] These data suggest that younger children have greater potential for myocardial regeneration.

There are several reports of preclinical studies using rat or pig models of chronic MI that demonstrate the safety and feasibility of cardiac progenitor cell transplantation.[32-34] Transplanted cells significantly decreased infarct size and improved cardiac function. One study showed that transplanted cardiac progenitor cells have 8-fold greater efficacy of cardiac differentiation in vivo compared with BMCs, suggesting strong regenerative ability of this cell type.[34]

Two phase I clinical trials using cardiac stem/progenitor cells have been completed and reported to date (Table 2). In the SCIPIO trial, autologous c-kit-positive cardiac stem cells (CSCs) were administered by intracoronary infusion in patients with left ventricular dysfunction after coronary artery bypass grafting.[35] Although LVEF did not change in control patients, CSC-treated patients showed an increase in LVEF (30.3% to 38.5%) at 4 months after infusion, which was associated with decreased infarct size. This cardiac function improvement was maintained at 1 year. In the CADUCEUS trial, CDCs were infused into the coronary artery in patients after MI.[36] MRI analysis of these patients showed a reduction in scar mass and increases in viable heart mass and regional systolic wall thickening. However, LVEF did not differ between the control group and the CDC-treated group.

Preclinical Studies Using Pressure-Overloaded Right Heart Model

Increased pressure or volume overload is a key feature of congenital heart disease, particularly in single ventricle physiology with right ventricle morphology. Although it is difficult to make an animal model of congenital heart disease that mimics univentricular hearts, a pressure-overload right-heart model using pulmonary artery (PA) banding is a well-established animal model and might be useful to evaluate the safety and efficacy of cell transplantation in the setting of single ventricular lesions.

Hoashi et al. demonstrated that skeletal myoblast sheet transplantation improved diastolic dysfunction and suppressed ventricular fibrosis with increased capillary density in a rat PA banding model.[37] Two groups have reported cell transplantation in an ovine model of PA banding. In one study, skeletal muscle precursor cell injection resulted in successful engraftment that did not contribute to improvement of cardiac function.[38] In another study, injected human cord blood stem cells engrafted and augmented both systolic and diastolic function of the right ventricle.[39]

In our study using a rat PA banding model, after intracoronary infusion of rat CDCs, histological investigation showed obvious engraftment of injected CDCs within the right ventricle. The reduction of cardiac fibrosis resulted in substantial cardiomyocyte regeneration. Taken together, these results suggest that cellular therapy might be effective for treatment of heart failure in patients with congenital heart disease.

Transcoronary Infusion of Cardiac Progenitor Cells in Children with HLHS

One of the subtypes of single ventricle physiology, HLHS is characterized by a variable degree of underdevelopment of the left ventricle and its components. HLHS is still one of the most high-risk lesions in children with congenital heart disease, and the survival rate is around 65% at 5 years of age.[40]

We designed a clinical trial to evaluate the safety and feasibility of transcoronary infusion of autologous CDCs for heart failure in children with HLHS. In our protocol, atrial tissue was obtained during Glenn or Fontan operation to isolate CDCs. The cells were cultured to reach a cell number of 30,000 per kg of body weight and then infused into the coronary artery by cardiac catheterization 1 month after the surgical procedure (Figure 1).

This protocol has the following advantages: (1) Cardiac progenitor cells are somatic stem cells with the highest potential for regeneration of cardiac muscles among the stem cells that

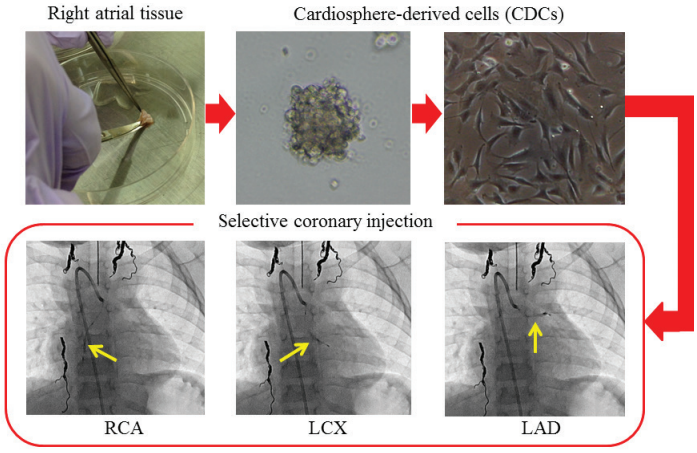

Figure 1. A schema of cardiosphere-derived cell isolation and transplantation. RCA: right coronary artery; LCX: left circumflex artery; LAD: left anterior descending artery

Target diseases	No. of patients	Age of patients	Follow-up (months)	Cell type	Delivery route	Outcome
Myocardial infarction SCIPIO[35]	23	Treated 56.0 ± 8.8 Control 57.3 ± 8.9	12	CSC	IC	LVEF increased 8.2%
Myocardial infarction CADUCEUS[36]	25	Treated 54.0 ± 2.5 Control 50.9 ± 5.5	12	CDC	IC	No effect on LVEF, scar reduction

Table 2. Clinical trials of cell therapy using cardiac progenitor cells. CSC: cardiac stem cell; CDC: cardiosphere-derived cell; LVEF: left ventricular ejection fraction.

have been reported to date and are transplantable into the same individuals; (2) cardiac progenitor cells isolated from younger children are more abundant and have greater potential for myocardial regeneration than those from adults; (3) tissue specimens are obtained during cardiac surgery, so an additional invasive procedure such as bone marrow aspiration is not necessary; and (4) the number of progenitor cells can be standardized to a constant number on transplantation by implementing the in vitro culture process.

The phase I controlled trial (Transcoronary Infusion of Cardiac Progenitor Cells in Patients with Single Ventricle Physiology: TICAP) was completed in January 2013 (Table 1). No adverse events attributable to the cell transplantation were noted. We found that right ventricular systolic function was significantly improved in seven CDC-treated patients compared with the level in the control group. These encouraging results indicate that intracoronary infusion of autologous CDCs in children with single ventricle physiology is safe and effective, warranting a further, larger phase II study. We then started the phase II study (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease: PERSEUS) in April 2013. To verify the efficacy, a total of 34 patients are randomly assigned to the treatment or control group in a 1:1 ratio. Cardiac ejection fraction is assessed by echocardiography, ventriculography, and cardiac MRI at 3 and 12 months after treatment and compared with that of the control group. Using cardiac magnetic resonance late gadolinium enhancement, we also assess myocardial fibrosis, which was not investigated in the phase I study.

Conclusion

Despite advances in surgical and medical management, the long-term prognosis of patients with single ventricle physiology remains unsatisfactory. Stem cell therapy seems to be safe and effective in children with a single ventricle. Although the effects appear to be greater in children than in adults, further studies including large randomized trials are necessary to verify the efficacy of stem cell therapy.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement, and Dr. Oh reported having patents for cardiac stem cell purification and therapy.

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