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First US babies treated in study of adult stem cell therapy for congenital heart disease

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In a first-in-children randomized clinical study, medical researchers at the University of Maryland School of Medicine (UM SOM) and the Interdisciplinary Stem Cell Institute (ISCI) at the University of Miami Miller School of Medicine have begun testing to see whether adult stem cells derived from bone marrow benefit children with the congenital heart defect hypoplastic left heart syndrome (HLHS).

UM SOM surgeons are injecting the cells into the babies' hearts during open-heart operations at the University of Maryland Medical Center. ISCI is supplying the stem cells for the procedures.

Even with extensive surgical treatments, HLHS babies still do not have optimal outcomes. The researchers hope the cells will increase the babies' chances of survival as HLHS limits the heart's ability to pump blood from the heart to the body.

"The premise of this clinical trial is to boost or regenerate the right ventricle, the only ventricle in these babies, to make it pump as strongly as a normal left ventricle," says lead researcher Sunjay Kaushal, MD, PhD, associate professor of surgery, University of Maryland School of Medicine and director, pediatric cardiac surgery, University of Maryland Medical Center. "We are hoping this therapy will be a game-changer for these patients."

Kaushal says the first two patients, who were both four-months-old when the stem cells were injected, are doing well after their surgery.

Mesenchymal Stem Cells

This is the first HLHS research in the United States to use stem cells known as allogeneic mesenchymal stem cells (MSC). Allogeneic cells can be used in other human beings without creating an immune response, which could cause the body to reject the cells. Additionally, these cells are a type of adult stem cell (found in both children and adults), unspecialized cells that can develop into tissue- or organ-specific cells. MSCs can be harvested in advance, expanded in culture, and stored for use later.

The allogeneic nature of the MSCs makes it possible for stem cells from one bone marrow donor to provide all the stem cells for this study. Researchers elsewhere are taking a different approach to strengthen the HLHS heart, with autologous cells, stem cells taken from the HLHS patient's own umbilical cord, for use in that specific patient.

In adult patients, MSCs in the heart have been shown to reduce scar tissue, reduce inflammation, cause new small vessels to grow, and stimulate the heart to regenerate itself, causing heart muscle cells and cardiac stem cells to grow.

"We've had incredible results in using mesenchymal stem cells to regenerate damaged heart muscle in adults," says Joshua M. Hare, MD, ISCI founding director and sponsor of the study. "This is the first time these types of cells are being used in infants, so this is very exciting."

The Interdisciplinary Stem Cell Institute has grown from a local research center to a national cell manufacturing facility. ISCI provides cells for the Cardiovascular Cell Therapy Research Network, has been named a Production Assistance for Cellular Therapies Center by the National Heart, Lung and Blood Institute, and has been conducting research in stem cell use for cardiovascular repair since 2008.

Study Details

HLHS is one of the most challenging and complex congenital heart diseases to treat. The Centers for Disease Control and Prevention (CDC) estimates that about 960 babies in the United States are born each year with HLHS. For unknown reasons, the heart's main pumping chamber, the left ventricle, does not develop completely during a critical growth period just prior to birth. The right ventricle normally pumps blood to the lungs at low pressure to be oxygenated, while the left ventricle pushes blood at high pressure through the aorta to the entire body. In children with HLHS, the right heart assumes the extra workload, temporarily supporting the circulation to both the lungs and body. That stress can cause the right heart to fail and the baby to die.

Current HLHS treatment options are either a heart transplant or a series of three open-heart reconstructive surgical procedures to connect the left and right sides of the heart. However, even with a transplant or the reconstructive surgical series, children with HLHS have an average five-year survival of only 50-60 percent.

In this Phase 1 safety and efficacy study, allogeneic MSCs are injected into the heart muscle during the second of the three reconstructive surgeries, typically performed at approximately four months of age.

A total of 30 patients with HLHS will be enrolled in the study. Fifteen patients will receive six-to-eight stem cell injections each, based on the size of the heart, while 15 control patients will not receive the cells. This is an open-label trial, in which researchers and participant families will know whether or not the cells are administered.

Basic Science

Kaushal laid the groundwork for this trial eight years ago as he began exploring the possibilities of stem cells to strengthen children's hearts. Kaushal says he and his team developed many models trying to understand how these cells work in the laboratory before moving to a clinical application. "There's a lot of basic science behind what we're doing. I want to make sure that what we pursue is rigorous in the laboratory, to make sure that we're providing the best therapy for these little kids."

Several researchers at the School of Medicine's University of Maryland Center for Stem Cell Biology & Regenerative Medicine have added their expertise to the effort, collaborating with Dr. Kaushal to understand and develop stem cell therapy for children with heart failure.

"Dr. Kaushal and colleagues have discovered that the failing neonatal heart is actually a rich source of cardiac stem cells, but the existing stem cells in the hearts of these babies are not sufficient to overcome HLHS," says Curt I. Civin, MD, professor of pediatrics and physiology, director of the Center for Stem Cell Biology & Regenerative Medicine, and Associate Dean for Research at the University of Maryland School of Medicine. "We are close to understanding one mechanism underlying this insufficiency. This line of research is a key part of our quest to use stem cells to repair, cure and prevent severe diseases in children and adults."

In previously published research, Kaushal demonstrated that mesenchymal stem cells can restore function in a pre-clinical model replicating many of the features of HLHS. The stem cells remodeled the heart muscle (myocardium) similar to normal myocardium. Stem cells in the heart may also secrete growth factors conducive to forming heart muscle and keeping the muscle from dying. "These key findings suggested these cells would work for HLHS patients," says Kaushal.

While stem cells have been used to regenerate adult hearts, Kaushal says improvements have been marginal. His research suggests results may be better in pediatric hearts: "The heart is able to remodel better in a younger patient than an older patient, because the body is still growing, good things are going on, and things are not deteriorating."

Civin, a pediatric oncologist, says his very first patient as a pediatric intern-in-training years ago was an infant with HLHS. "I've seen how devastating HLHS can be for babies and their families. I'm thrilled with the launch of this first-in-children stem cell therapeutic trial, and look forward to the patient outcomes."

The Department of Surgery at the University of Maryland School of Medicine is providing funding for the clinical costs associated with this trial. "Dr. Kaushal's research will give families with a devastating diagnosis hope for a better outcome for their child," says Stephen T. Bartlett, MD, the Peter Angelos Distinguished Professor; Chair of the Department of Surgery at the University of Maryland School of Medicine; and Surgeon-in-Chief and Executive Vice President of the University of Maryland Medical System. "The Department of Surgery's funding of this project demonstrates the critical need and the promise this research holds for a very at-risk population who only have a 50/50 shot at survival with current treatment protocols."

"This novel therapeutic approach exemplifies how our faculty are unrelenting in their search for new ways to improve the health of some of our tiniest and most vulnerable patients," says E. Albert Reece, MD, PhD, MBA, vice president for medical affairs, University of Maryland; the John Z. and Akiko K. Bowers Distinguished Professor; and dean, University of Maryland School of Medicine." This stem cell therapy may provide a new treatment option not just for patients with HLHS, but also for patients with other congenital heart problems."