The Rapidly Expanding Uses of Newborn Stem Cells

Newborn Stem Cells, Issue 2

Cord Blood Stem Cells Find New Uses in Regenerative Medicine

Nearly 80 disorders, including leukemia, immune deficiencies, and others, have been treated with umbilical cord blood–derived stem cells.[1] Research continues to identify advanced applications for these stem cells. The newest research is leading toward exciting applications for cord blood stem cells in the field of regenerative medicine.[1,2]

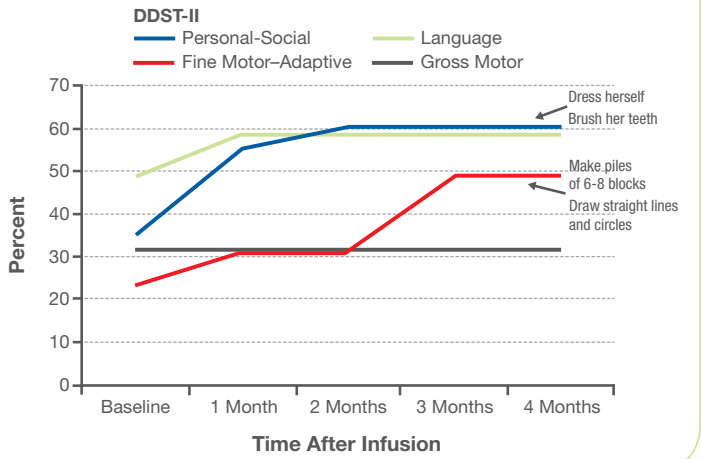
The disorders treated to date—mostly hematologic or oncologic—have seen success with cord blood transplantation because umbilical cord blood contains hematopoietic stem cells (HSCs) capable of forming healthy new blood cells.[3] Potential applications of cord blood stem cells in regenerative medicine extend beyond hematologic and oncologic disorders, as illustrated by the examples of cerebral palsy and type 1 diabetes mellitus.[4,5]

Cerebral Palsy

Encouraged by evidence suggesting that cord blood stem cells can produce cytokines that help restore brain function, researchers are now investigating the use of these cells for the treatment of neurological disorders in children **(Figure 1)**.[4] The results of another promising study, in which two toddlers with cerebral palsy received autologous cord blood stem cell infusions along with low-dose granulocyte colony-stimulating factor (G-CSF), were published by Papadopoulos et al.[6] One child received G-CSF about 1 year after infusion and the other received it 5 days prior to the infusion. Both children showed significant motor function improvements over time. The first child was unable to stand or walk at age 19 months, prior to the infusion, but was able to stand assisted within 7 weeks of receiving his own cord blood. As of the publication date, this same child, aged 36 months, could run and walk with little assistance and showed reduced spasticity in both the upper and lower limbs. The second child was a 15-month-old boy who was able to stand only with the help of a brace at the time of infusion. By the end of the study, he was able to walk and swim and also displayed reduced spasticity in his upper limbs and hands. Both children improved from level III to level I on the Gross Motor Function Classification System used for children with cerebral palsy, indicating significant normalization of motor function.[6]

> Cord blood stem cells can help improve the motor functions of children with cerebral palsy

Figure 1. Neurodevelopmental Evaluation After Cord Blood Infusion



In a 5-year-old girl with cerebral palsy, functional improvements were seen 1 month after autologous cord blood stem cells were infused. Improvements were seen in the personal-social, fine motor-adaptive, and language scales of the Denver Development Screening Test II (DDST-II).[4]

In an FDA-sanctioned, phase 2 clinical trial, Dr. Kurtzberg and her colleagues at Duke University are currently studying the effects of autologous infusions of cord blood stem cells on

neuronal repair and functional status in a larger group of children (aged 1 to 6 years) with cerebral palsy.[7] This randomized, blinded, controlled crossover clinical trial is the first of its kind.[8] During the course of the trial, every study participant will receive an infusion of his or her own banked cord blood. The goal is to enroll 120 patients in the trial, which had its first patient infused in September 2010.[7,8] Investigators hypothesized that treating children with their own cord blood will facilitate neuronal repair and ultimately result in improved function in patients with cerebral palsy.[7] If the results are positive, this randomized controlled trial will further substantiate the potential benefit of cord blood stem cells in cerebral palsy.[8]

Diabetes

In addition to their use in neurologic conditions such as cerebral palsy, HSCs from cord blood are also being studied to help preserve β-cell function in type 1 diabetes. In an early, uncontrolled, observational, phase 1 pilot study, Haller et al provided autologous cord blood infusions to 24 children with newly diagnosed type 1 diabetes to determine whether the infused cells could overcome the immunological processes of diabetes and preserve the body's remaining ability to produce insulin endogenously.[9] No treatment-related adverse events were reported in association with the infusions. Unfortunately, the infusions were unable to preserve C-peptide levels 2 years later.[10] Although a control group was not included in the study, comparison with historical controls failed to identify evidence of efficacy, with similar patterns of hemoglobin A1C levels and requirements for insulin in the infused patients as in the controls.[5] However, the treatment did have some positive effects: flow cytometry revealed an increase in the number of T regulatory cells (P=0.04) 6 months post-infusion.[10] Despite the disappointing efficacy findings, the investigators were encouraged enough by the safety and feasibility of the autologous cord blood infusions from the 1-year interim results and by the favorable T-cell change that in March 2009 they launched a phase 2 dose-response study to expand upon this work.[11]

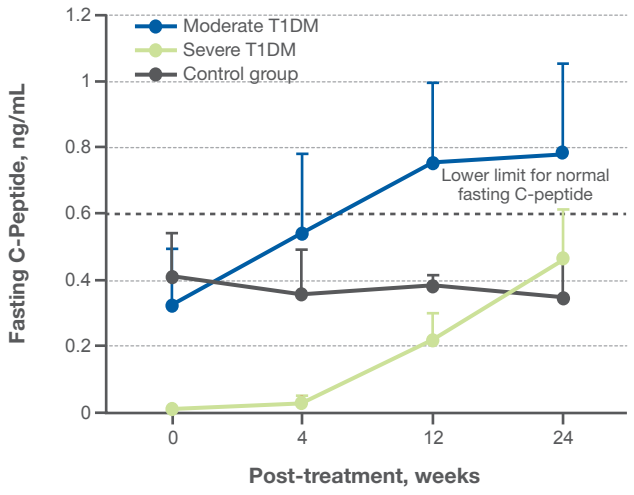
This follow-up trial, co-sponsored by the National Institutes of Health and the Juvenile Diabetes Research Foundation, aims to build on the phase 1 pilot study by adding vitamin D and omega-3 fatty acid supplementation to the autologous cord blood treatment plan. The hypothesis is that this regimen may augment the patient's immune response and preserve β-cell function in these patients. The study is estimated to be completed this year.[11]

In another diabetes study, investigators used a novel "stem cell educator therapy" approach in an attempt to overcome the autoimmune component of diabetes by "re-educating" the patient's own lymphocytes using co-cultured allogeneic cord blood stem cells. The lymphocytes of 15 patients with type 1 diabetes were separated from the whole blood. The

> Stem cell educator therapy has restored damaged cellular function in type 1 diabetes

lymphocytes were co-cultured briefly with adherent cord blood stem cells from healthy donors before the blood was returned to the patient's circulation (n=12). This process, with the exception of the stem cell co-culture step, was also used in a control group (n=3). According to the investigators, human leukocyte antigen matching was not necessary prior to treating patients with stem cell educator therapy because no cord blood stem cells were actually transferred to the patients and because of the very low immunogenicity associated with these cells. Patients with both moderate and severe type 1 diabetes who received "educated" stem cells experienced a reduced daily need for insulin as well as improvement in fasting C-peptide levels **(Figure 2)**, indicating

Figure 2. Stem Cell Therapy Improved Fasting C-Peptide Levels[12]



promise for the regenerative properties of cord blood stem cells to help restore cellular processes damaged by diabetes.[12] The T regulatory cell findings from the Haller et al trial combined with the favorable results from this stem cell educator trial utilizing cord blood stem cells underline the importance of addressing the immune dysfunction in patients with diabetes.[10,12] In these studies, stem cells have shown some promise in being able to ameliorate this damage.

Cord Tissue MSCs Have Shown Potential in the Preclinical Setting

Due to their capacity for differentiation, naive state, and easy expansion, mesenchymal stem cells (MSCs) from umbilical cord tissue have great potential as regenerative therapies.[13,14,15] Further, MSCs can exert immune modulatory, antitumor, and angiogenic effects.[16,17,18,19] Preclinical studies have shown promise in many areas **(Table 1)**.

Table 1. Potential Therapeutic Applications for Cord Tissue MSCs Based on Preclinical Studies

Therapeutic Area	Therapeutic Mechanism
Parkinson's disease	MSCs may stimulate the production of new neurons to restore the damaged dopamine-driven motor system.[14]
Stroke	MSCs may revascularize the stroke-damaged area of the brain, reducing the extent of brain injury.[16]
Lung cancer	MSCs have the ability to interfere with tumor growth in induced lung cancer in mice.[17]
Sports-related injuries involving cartilage damage	MSCs may repair these injuries through cartilage tissue engineering.[20]
Liver fibrosis	MSCs may reverse liver fibrosis by secreting cytokines, reducing the activation of hepatic fibrosis-inducing cells and enhancing liver cell repair.[18]
Inflammatory disorders	MSCs may reduce inflammation, including histologic and structural improvements in joint damage of rheumatoid arthritis.[19]
Type 1 diabetes	MSCs have the potential to differentiate into insulin-secreting cells which can help normalize blood sugar.[15]

The Latest in Stem Cell Research

Perivascular MSCs Have Been Shown to Reduce Cardiac Inflammation Post-MI in the Preclinical Setting

After myocardial infarction (MI), monocyte/macrophage infiltration into the myocardium reflects a proinflammatory profile followed by an anti-inflammatory response.[21] This initial increase in inflammation can lead to deleterious cardiac remodeling, which is the leading cause of heart failure and death.[22] Dayan and colleagues first induced MIs in mice, then intravenously administered medium or human umbilical cord perivascular MSCs.[21] MSCs reduced overall monocyte/macrophage levels circulating in the heart tissue, whereas they significantly decreased leukocyte infiltration and significantly increased monocyte/macrophage infiltration to the infarcted myocardial tissue specifically. Most importantly, an improvement in short-term cardiac function, as evidenced by increased left ventricular fractional shortening in cell-treated mice compared with control mice at 2 and 4 weeks, was also observed. In addition, MSCs led to a decrease in long-term cardiac remodeling, shown by significant reductions in septum thickness in the cell-treated groups compared with medium-treated mice at 16 weeks. After MI, MSCs from umbilical cord perivascular regions mediated a monocyte/macrophage switch to an anti-inflammatory state that may be associated with improvements in cardiac function.[21]

Newborn Stem Cell Collection Tip

When collecting cord blood, if there is still cord blood in the vein, but the blood has ***stopped*** flowing,

- Close off the cord blood collection system
- Select another site to draw from
- Clamp the cord directly below that site
- ***Re-clean the cord***
- Reinsert the needle into the new location
- Open the collection system again to start the flow of blood

Did You Know?

Red Blood Cells Can Be Included or Depleted From Newborn Stem Cell Units

When processing a unit of cord blood stem cells prior to storage, red blood cells are depleted (called red blood cell–depleted units), partially depleted, or left alone (called red blood cell–replete units).[23] When a transplantation center is considering the available cord blood stem cell units, one of the factors to compare is the total nucleated cell dose, or TNC count. If the potential units are replete with red blood cells, application of a correction factor to the cell count may be necessary to account for the higher reported nucleated red blood cell and granulocyte content inherent in the red blood cell–replete units. In order to accurately compare the TNC count with that of units that have had red blood cells depleted, transplant centers may correct the TNC count of the red blood cell–containing unit downward by 25% to 30%.[23,24] It is important to weigh all of the aspects of processing to determine the optimal quality of newborn stem cell products. The United States Food and Drug Administration recommends that prior to cryopreservation, the cord blood unit should be depleted of plasma and red blood cells.[25] For cord blood units that were cryopreserved as red blood cell–replete, the National Marrow Donor Program recommends the unit be prepared by washing the red blood cells prior to infusion. Additionally, the Blood and Marrow Transplant Clinical Trials Network requires washing the units post-thaw and prior to infusion.[26] The removal of red blood cells is the preferred processing method used in both family and public cord blood banking **(Table 2)**.[27]

Table 2. Red Blood Cell Processes Used by Some of the Leading Newborn Stem Cell Banks

National Family Bank	Removes Red Blood Cells	
	Yes	No
ViaCord[23,28]	✓	
CBR[29,30]	✓	
Cryo-Cell[31,32]	✓	
LifeBank[33]	✓	
StemCyte[34]		✓
National Public Bank	**Removes Red Blood Cells**	
	Yes	**No**
Carolinas Cord Blood Bank[35]	✓	
MD Anderson[23,28,36]	✓	
New York Blood Center[32]	✓	
StemCyte[34]		✓
St. Louis Cord Blood Bank[37]	✓	

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