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UMBILICAL CORD STEM CELL THERAPY FOR CEREBRAL PALSY

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CASE REPORT

ABSTRACT. THE AUTHORS HYPOTHESIZE that stem/progenitor cells from umbilical cord blood are safe and promising for various brain injuries and disorders. A six month pilot study predicated on parental observations and completed questionnaires concerning the responses of cerebral palsy-stricken children to treatment with umbilical cord stem cells was launched during 2004. As part of this Mexican study, eight children (3–12 years of age) diagnosed with cerebral palsy underwent transplants with 1.5 million stem/progenitor cells (CD34+ and CD133+) that had been purified and expanded from the American Association of Blood Banks (AABB)-certified human umbilical cord blood. According to parent tendered observational reports, none of the children had graft versus host reactions. Eight out of eight children showed some improvement in mobility and/or cognitive function. Six children (75%) were rated as improving in muscle tone, hip movement, leg movement, rolling to the side, balancing while sitting and balancing while standing by the end of the six month follow up. Further research, correlating parent ratings with tomography studies and physical therapy evaluations, seems warranted.

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1. INTRODUCTION

The umbilical cord/placenta from a newborn baby usually contains approximately 300,000 stem cells, including CD34+ and CD133+ cells. These stem cells pose no ethical challenge, and appear to be safe (when properly tested), versatile and promising for brain injuries and disorders.

ETHICS. Umbilical cord stem cells are widely deemed ethical insofar as there is no loss of potential life from their use. The cord/placenta units can be harvested for their stem cell load as a form of "life assurance" for the donor's baby's future health challenges as well as for those of other children and adults.

SAFETY. Umbilical cord blood certified by the American Association of Blood Banks (AABB) has a sixteen year track record of safety.

(*a*) WHOLE CORD BLOOD. Umbilical cord blood (which includes stem cells) has been used for sixteen years in the United States for leukemia [1], breast cancer [2], prostate cancer, ovarian cancer, aplastic anemia [3], Fanconi's anemia [4], immune disorders, storage diseases [3], and bone marrow reconstruction after cancer irradiation [5].

Whole cord blood produces significantly less graft-versus-host disease (GVHD) than transplantations with bone marrow or adult hematopoietic cells [6-9]. Risks are significantly reduced even with ABO blood group incompatibility [10].

In 2002, McKeena and associates reported on the graft versus host reactions from 59 patients who received umbilical cord blood transplants (including red blood cells, white blood cells, platelets, and stem cells). The patients were pretreated with acetaminophen and diphenhydramine. There were no moderate or severe reactions though some patients experienced mild reactions that included hypertension (24%), nausea (10%), vomiting (5%), unusual taste or smell (5%), headache (5%), bradycardia (2%), cough (2%), back (2%) or abdominal (2%) pain and transient thirst (2%). None of the patients experienced fever, chills, flushing, hives, dyspnea, bronco-spasm, or chest pain and there was no clinical or laboratory evidence of hemolysis [11].

(*b*) ISOLATED CD34+ CELLS. Handgretinger and colleagues showed in 2001 that CD34+ progenitor cells could be extracted from donor peripheral blood for HLA-mismatched stem cell transplantation without graft versus host disease. Megadoses of highly purified mismatched CD34+ progenitor cells were given to 32 children without pharmacological immunosuppression. The authors concluded that this procedure offers a promising therapeutic option for children without bone marrow donors [12]. Since then Benesch used highly purified CD34+ stem/progenitor cell transplants in children with refractory severe aplastic anaemia and reported no evidence of GVHD [13].

(*c*) ISOLATED STEM/PROGENITOR CELLS FROM CORD BLOOD. Separating stem/progenitor cells (magnetic bead technologies can be used) from the red and white blood cells and platelets removes potential antigens and immune cells. This stem cell separation contributes to a lower risk of graft versus host reactions, even with mismatched donors and recipients [14-16]. In addition, expanding the stem cells to several million cells per treatment can further minimize and eradicate graft versus host reactions [17,18]. This low to nil reaction is important in neurological conditions because immune suppressants can have detrimental effects on learning and memory. In 1996, Cool reported on neurological evaluations at the University of Iowa on children before and after immunosuppression with chemoradiation therapy and bone marrow transplants. Four years post-treatment, there was still evidence of declining IQ, achievement, memory and fine motor skills [19].

UMBILICAL CORD STEM CELLS APPEAR TO BE VERSATILE. Umbilical cord stem cells appear to migrate to where they are needed (attracted by cytokine signals from areas of inflammation such as stromal derived factor-1α). Cord stem cells can be used for ischemic/hypoxic conditions since they have the ability to initiate the formation of new blood vessels, thereby increasing the delivery of oxygen and nutrients to injured and hypoxic tissue [20]. In addition, cord blood stem cells (CD34+) including CD133+ cells, have the potential of becoming endothelial cells, hepatocytes, and osteoblast-like cells, neurons and glia cells [21-29].

Patients treated for brain and neurologic disorders outside the U.S. report unexpected side benefits such as renewed hair growth and hair color, relief from arthritic pain, reduced infections, and greater emotional equilibrium and contentment for months after umbilical cord stem cell therapy.

UMBILICAL CORD STEM CELLS SHOW PROMISE FOR NEUROLOGICAL INJURIES AND DISORDERS. Umbilical cord stem cells are being used to treat neurological injuries and disorders in various countries. Stem cells may assist neural repair by stimulating synthesis of growth factors [30,31], serving as chaperone or nurse cells to injured tissues, and/or by facilitating neurogenesis.

(*a*) CORD BLOOD. Ende [32,33] and Garbuzova-Davis [34] demonstrated that umbilical cord blood could increase life span in mice models of Huntington's Disease, Alzheimer's Disease, and Amyotropic Lateral Sclerosis. Lu and associates [35] also found significant improvements from human cord blood in animal models with traumatic brain injury. And when Chen and associates [36] gave human umbilical cord blood intravenously to rat models for stroke paralysis, they showed significant improvement in motor function within 24 hours. This 2001 study also demonstrated that cord blood stem/progenitor cells could enter the brain, migrate to the injury and promote functional recovery in a brain injury.

(*b*) STEM CELLS ISOLATED FROM CORD BLOOD. Umbilical cord CD34+ cells show therapeutic potential for treating neurodegenerative diseases and trauma [25,28,37]. Vendrame [38], Taguchi [39], Peterson [22], Newman [40,41] and Willing [42,43] have reported neurological improvements in animal models of stroke using human umbilical cord blood stem cells. Saporta and associates reported on the ability of human umbilical cord stem cells to migrate to the spinal cord injury in animals and significantly reduced motor and neurological deficits in an open-field test [44].

(*c*) STEM CELL THERAPIES USING UMBILICAL CORD CELLS. The International Spinal Cord Regeneration Center has been involved in research-oriented application of umbilical cord stem cells since early 2003. Currently many cord blood stem cell subtypes such as CD34+/CD133, CD34-/45+, mesenchymals and primitive neurogenic progenitors are given by various means including subcutaneous injection, IV drip and intra-arterial catheter infusion. Patient responses indicate that ocular disorders such as macular degeneration and diabetic retinopathy and neurologic challenges such as cerebral palsy experience the most dramatic improvements. Patients with multiple sclerosis and chronic stroke show evidence of moderate benefits, especially if the stem cell therapy is used in conjunction with a total rehabilitation program that supports a healthy tissue environment conducive to stem cell activity.

2. PRELIMINARY OBSERVATIONS WITH CEREBRAL PALSY

Cerebral palsy is a disorder caused by damage to the brain during pregnancy, delivery or shortly after birth that affects about 500,000 children in the U.S. alone. It is characterized by muscle spasticity, muscle weakness, uncontrolled movements, impaired mobility, speech impairment and/or challenges in eating, dressing, bathing, etc. Movement dysfunction is often accompanied by seizures, visual impairment, hearing loss, osteoporosis, learning disabilities, and behavior problems [45]. Risk factors for cerebral palsy include prenatal anemia, improper nutrition, infections, x-rays, premature delivery. Hypoxia and ischemia are also major risk factors prenatally and during delivery [46,47].

SUPPORTIVE OBSERVATIONS. In the latter part of 2002, three (3) of the coauthors (Steenblock, Payne, Darnall) heard about patients with neurological disorders being treated with stem cells isolated and expanded from umbilical cord blood. Though initially skeptical about the claims being made about the treatment's safety and effectiveness, we began to interview some of these patients, contact physicians doing this work and started sending simple questionnaires to people who were going to other countries for these stem cell treatments. The best overall responses were apparently taking place in children with cerebral palsy. In addition, graft versus host reactions had not been reported by the approximately 100 children and

adults we ultimately interviewed who had been treated (outside the USA) with purified umbilical cord derived stem/progenitor cells. This line of inquiry brought Steenblock Research Institute into contact with Fernando Ramirez, M.D., who was involved in using cord blood stem cells for research-oriented applications under a special license issued him by the Mexican Ministry of Health. As a result of dialog between Steenblock Research Institute and Dr. Fernando Ramirez, a pilot study was proposed and designed by Dr. Ramirez with input and technical support from the SRI. The study protocol was approved by an independent committee for clinical research at Dr. Ramirez's institute (U.S. equivalent Investigational Review Board) as being in conformity with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects.

Eight children (aged 3–12) with cerebral palsy were admitted to the pilot study which was launched during January 2004. This report is the result of parental ratings of these children tendered prior to and then at regular intervals following their treatment with multipotent stem cells isolated and expanded from AABB certified umbilical cord blood.

3. METHODS

The cord blood was donated with the consent of the mother and safety tested for a panel of infections in accordance with American Association of Blood Banks (AABB) standards.

The stem/progenitor cells were isolated from the umbilical cord blood using a magnetic bead separation process and were then expanded over a three week period until they reach confluence. Eighty-five percent of the stem cells were primitive CD133+ stem cells, which have the ability to promote neural growth. The cells were harvested and aliquoted into vials in lots of 1.5 million, to which was added a standard cryoprotectant formula. These vials were frozen in liquid nitrogen until used.

Children of both sexes were considered for inclusion in the study who were between ages 6 months to 12 years, who had their cerebral palsy status diagnosed by a pediatric neurologist, and who had no complicating infections, trauma, injury or wounds or inflammatory conditions including dental abscesses or gum disease (as this might generate cytokine signals such stromal derived factor-1α which attracts stem cells). All candidates were screened by their primary care physicians and dentists for diseases and conditions that might "decoy" stem cells from the target organ (brain). Those that were not free of such diseases and conditions were immediately excluded from the pool of candidates. Ultimately eight children with the major cerebral palsy forms, e.g., spastic (pyramidal), non-spastic (extrapyramidal), and mixed were selected for inclusion in the study.

Parents of the eight CP children in the study were thoroughly briefed concerning the study protocols and subsequently gave informed (written) consent for their children to have stem cell therapy using purified umbilical cord blood stem cells. The parents also consented to fill out questionnaires before the stem cell treatment, and one month, three months and six months following the transplant which were entrusted by Ramirez to Steenblock Research Institute staff for tabulation and statistical analysis. All of these children had already been treated with various conventional therapies in previous years and their neurological status was considered stable by both their parents and therapists. The children continued all customary therapies, e.g., physical therapy, speech therapy, etc., as before the treatment. Evaluations of neurologic, speech, visual and other parameters post-treatment were done by the children's personal physicians and therapists with copies furnished to the research team.

The transplant procedure consisted of a simple subcutaneous intramuscular injection in fatty tissue near the umbilicus. The subjects were then observed for any adverse reactions for at least an hour and then released.

THE QUESTIONNAIRE. The questionnaire included graft versus host symptoms as well as fine motor, gross motor, self-help, social and cognitive behaviors. There were 78 questions and space for

TABLE 1. SYMPTOM IMPROVEMENT AT SIX MONTHS POST-CORD STEM CELL THERAPY.

FUNCTION	NOT IMPROVED	SLIGHTLY IMPROVED	MODERATELY IMPROVED	SIGNIFICANTLY IMPROVED	TOTAL IMPROVEMENT
BALANCE WHILE STANDING	2 (25%)	1 (12.5%)	4 (50%)	1 (12.5%)	6 (75%)
ROLL TO RIGHT/LEFT	2 (25%)	2 (25%)	3 (37.5%)	1 (12.5%)	6 (75%)
BALANCE WHILE SITTING	2 (25%)	2 (25%)	3 (37.5%)	1 (12.5%)	6 (75%)
MUSCLE TONE	2 (25%)	2 (25%)	4 (50%)	0	6 (75%)
LEG MOVEMENT	2 (25%)	3 (37.5%)	3 (37.5%)	0	6 (75%)
HIP MOVEMENT	2 (25%)	3 (37.5%)	3 (37.5%)	0	6 (75%)
BALANCE WHILE WALKING	3 (37.5%)	0	5 (62.5%)	0	5 (62.5)
UNDERSTANDING	3 (37.5%)	2 (25%)	3 (37.5%)	0	5 (62.5)
SPEECH	4 (50%)	1 (12.5%)	1 (12.5%)	2 (25%)	4 (50%)
THINKING	4 (50%)	2 (25%)	2 (25%)	0	4 (50%)
ARM MOBILITY	4 (50%)	1 (12.5%)	3 (37.5%)	0	4 (50%)
HAND MOVEMENT	4 (50%)	1 (12.5%)	3 (37.5%)	0	4 (50%)
VISION	4 (50%)	1 (12.5%)	2 (25%)	1 (12.5%)	4 (50%)

comments.

Questions were taken from McKeena's report [11] on side effects from cord blood and included changes in heart rate and blood pressure, nausea, back pain, rashes, chills, excessive thirst, rapid breathing, headaches, etc. There was also a section on symptoms and symptom improvements.

4. RESULTS

4.1. GRAFT VERSUS HOST REACTIONS

In eight out of eight children, the parents reported no graft versus host symptoms from the umbilical cord derived purified stem cell transplants. One child experienced localized mild pain for three days where the injection was given. Three children needed more sleep in the weeks following the transplant and one child needed less sleep. No other reactions were reported. This is highly significant, since immunosuppressants, required for adult stem cell transplants, were not needed because the cells were devoid of red and white blood cells and antigens as well as expanded for greater safety.

4.2. SYMPTOM IMPROVEMENT

The data is summarized in TABLE 1. The average parent rating for all the questions concerning symptom improvement was 2.06 (moderate improvement). At the end of the six month follow-up, the parents were asked to give an overall rating for their child's progress. Five of the eight children (62%) were rated as showing significant improvement since the stem cell therapy, two children (25%) were rated as moderately improved and one child (12%) was rated as slightly improved. This child had experienced cold symptoms before the stem cell implant but had no infections in the six month period following it. Physician, physical therapist and speech therapist evaluations paralleled that of the parent's.

During the study one aphasic child started talking and one child who had been blind from birth due to optic nerve atrophy was able to see by month six post-treatment. Interestingly, an ophthalmologist who saw the child many months prior to his cord blood stem cell treatment reported that the child would never see. Four months after his injection he tracked a ball rolling across the living room of his family home. Two weeks later a second ophthalmologist at a major Florida university eye institute reported that the child could see and recommended glasses. These improvements were faithfully reported by the parents.

The main objective of this pilot study was to begin quantifying results, especially in terms of safety. Further studies are needed using a larger

group of subjects and correlating parent ratings with tomography studies and physical therapy evaluations.

5. CONCLUSION

The results from this preliminary observational pilot study suggest that umbilical cord stem cells may be a safe and promising treatment for children with cerebral palsy. While the exact mechanism underlying efficacy is as of yet not fully known, it has been conjectured by one of the coauthors (Payne) that human umbilical cord stem cells injected into adipose tissue stimulates synthesis of TNF-alpha which opens up the blood brain barrier, and Nerve Growth Factor which facilitates neurologic repair [48]. Currently, SRI's in-house laboratory is doing ELISA and other quantitative testing on pre- and post- treatment blood samples from patients undergoing human umbilical cord stem cell therapy at the Spinal Cord Regeneration Center in Tijuana, Mexico. Further, more rigorous research into the promise and utility of human umbilical cord stem cell use in addressing various neurologic disorders (and the mechanism or mechanisms underlying efficacy) including cerebral palsy, seems warranted.

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