**Umbilical Cord Blood Mononuclear Cell Therapy of Chronic Complete Spinal Cord Injury**

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We transplanted human leukocyte antigen (HLA≥4) matched umbilical cord blood mononuclear cells (UCBMNC) into 28 people with chronic complete spinal cord injury (SCI), 8 in Hong Kong (HK) and 20 in Kunming (KM).  The patients rangee in age from 2-20 years, averaging 14 years in HK and 7 years in KM.  In HK, 4 participants received four injections of 4-µliters of 100,000 cells/µliter (total 1.6 million UCBMNC) and another 4 received four 8-µliter injections (total 3.2 million UCBMNC).  Magnetic resonance diffusion tensor imaging (MR/DTI) revealed fibers growing across the injury site in two people at 6-12 months and reduced white matter gaps in the rest.  The participants received standard rehabilitation without locomotor training.  Several recovered 1-2 dermatomes of touch sensation but none recovered significant voluntary motor function or walking.  In KM, 4 participants received 4-µliter injections totaling 1.6 million UCBMNC, 4 received 8-µliter injections totaling 3.2 million cells, and 4 received 16-µliter injections totaling 6.4 million cells, 4 receive 6.4 millions cells and a 30 mg/kg bolus dose of methylprednisolone (MP), and 4 received the 6.4 millions cells, MP, plus a 6-week course of oral lithium carbonate titrated to 0.6-1.2 mM serum levels.  All but one participant had “complete” (American Spinal Injury Association Impairment Scale or AIS A) SCI with neurological levels of C5 through T11.  The one participant had a C3 neurological level and was motor incomplete (AIS C).  Before treatment, only 10% of the 20 participants could walk without assistance.  At 3-6 months, 15 of 20 (75%) of participants were walking 6 hours a day and 6 days a week; 35% without assistance and 40% with minimal assistance (a person walking behind with ropes to lock the knees in stance phase).  Three participants stopped training due to old tibial fractures in two and knee swelling in a third.  The participant with C3 incomplete SCI did not recover walking.   The Walking Index of Spinal Cord Injury (WISCI) indicated that 75% of participants could walk 10 meters at one year, 40% with assistance and 35% without assistance.  The Spinal Cord Independence Measure (SCIM) did not improve in HK but improved by 19.6±2.67 points (p<0.0005) in KM at one year.  Fourteen of 19 SCIM subscores (except feeding, grooming, respiration, outdoor respiration) improved significantly (p<0.05).   In addition, SCIM showed that 60% of participants no longer required help with urinary function at one year compared to only 10% before treatment and 55% no longer used catheters.  Likewise, 60% recovered regular bowels movements and no longer required assistance for bowel function, compared to only 10% before treatment.   Only 2 of 4 participants recovered walking after the lowest dose of 1.6 million cells, 8 of 8 participants that received 3.2 or 6.4 million cells recovered walking, 3 of 8 participants that received MP recovered walking, and 1 of 3 participants that received transplants, MP, and lithium walked.  We conclude that transplanting up to 6.4 million UCBMNC in spinal cord is safe, that the transplants encourage fibers grow across the injury site, and the treatment appears to restore walking, micturition, and defecation but only when participants receive intensive locomotor training.  The participants did not significantly improve their motor scores.  We hypothesize that the participants learned to activate central pattern generators for locomotion, micturition, and defecation.  These are programmed motor function in the lumbosacral spinal cord.  MP did not improve recovery.  MP and lithium together also did not appear to improve recovery, although only 3 participants received lithium because one mistakenly received placebo.  These results need to be confirmed in further clinical trials.  We propose phase II trials to assess UCBMNC transplants with and without lithium in China, India, and the U.S.  If these trials show that UCBMNC and lithium improves recovery, we will proceed to phase III trials to compare untethering surgery, surgery plus a 6-week course of lithium, surgery plus transplantation of 6.4 million UCBMNC, and surgery plus UCBMNC transplant plus lithium.   Otherwise, the phase III trials will compare only surgery and surgery plus UCMBNC transplants, followed by locomotor training.  To rule out the possibility that locomotor training alone can restore functional recovery, we are now doing a trial comparing effects of intensive locomotor training with untethering surgery or no surgery in 30 people with chronic complete SCI.