

Evaluation of the efficacy of allogeneic umbilical cord derived hematopoietic stem cells and mesenchymal stromal cells in patients with spastic cerebral palsy on developmental function , A Clinical trial phase II

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Brief Summary:

Background information: Cerebral palsy (CP) consisted of a group of developmental disability in the field of motor milestones. At the present time there is no standard curative medical or surgical treatment for it .Stem cell therapy is one of a new and hopeful therapeutic methods of therapy for CP.

Objectives :This study designed for the evaluation of safety and therapeutic effects of intrathecal hematopoietic (MNC) and mesenchymal stem cells (MHC) derived from allogeneic umbilical cord in change and probable improvement of developmental functions of spastic CP participants in comparison with control group .

Study design: 108 cases of Spastic CP patients between 4-14 years old that referred to Children's Medical Center affiliated to Tehran University of Medical Sciences and had our inclusion criteria selected and randomly divided in 3 groups of MNC, MHC and control participants. One intrathecal injection of stem cell was done for intervention groups and simulation of intrathecal injection without awareness of participants prepared for control group. All of the participants had a baseline brain neuroimaging and underwent a complete exams with our outcome measure scales and neurorehabilitation with similar protocol performed for both intervention and control groups. Follow up evaluations until 12 months and brain neuroimaging at the end of 12 months will be done for participants. This study is double blind and participants and evaluators are not aware of the groups.

Detailed description:

Background information:

Cerebral palsy (CP) is characterized by aberrant control of movement or posture of a patient, appearing early in life, and not the result of a recognized progressive or degenerative brain disease. CP is an umbrella term and represents a group of conditions (not a single disorder), has a broad range of expression with a static condition originally within the developing central nervous system.

CP is a disturbance of movement and or posture. CP is a static neurologic condition resulting from brain injury that occurs during the first two years of life.

CP can result from brain injury occurring during the prenatal, perinatal, or postnatal periods. Seventy to 80 percent of patients with CP have spastic clinical features. In developed countries CP occurs in approximately 2.5/1000 live births.

At present, conventional therapies for children with CP include medications, orthopedic and neurosurgical intervention and neurorehabilitation, but none of these treatments can fundamentally repair damaged neural cells. Stem cells have been investigated as a treatment for neurological damage since the 1990s. There are a number of developmental disorders that are considered targets for stem cell therapy. The most well-known and studied is CP. Stem cell therapy is a new and promising treatment of neurological disorders including CP. For using neurological trial, neurons and glial cells have been generated from Pluripotential stem cells and Multipotential somatic stem cells. There is little clinical trial for stem cell therapy in CP in Iran, that two of them have NCT number. Because of the increasing popularity of postnatal umbilical cord stem cell storage, the most easily accessible current source of stem cells in clinical trials is umbilical cord derived stem cells.

The least invasive source of stem cells, with the fewest ethical issues and with low

processing requirements, is umbilical cord blood (UCB). Safety of allogeneic UCB stem cells confirmed in several clinical trials. UCB is the most easily accessible current source of stem cells in our country. Well-matched allogeneic UCB has been used successfully in children for a number of decades so the risks of using this stem cell source are somewhat understood. There is evidence of in vitro differentiation of UCB into neuronal cells. Umbilical cord-derived mesenchymal stem cells is another source of effective and safe stem cells.

For the first time in our country we planned a trial of stem cells with mesenchymal stromal cells (MSC) derived from umbilical cord (UC), for the treatment of cerebral palsy.

Objectives:

This study designed for the evaluation of safety and therapeutic effects of intrathecal hematopoietic (MNC) and mesenchymal stem cells (MHC) derived from allogeneic umbilical cord in change and probable improvement of developmental functions of spastic CP participants in comparison with control group .

Study design:

Cases of Diparetic and Quadiparetic spastic CP between 4-14 years old selected among the patients referred to the pediatric neurology outpatient department of Children's Medical Center Hospital (CMC) affiliated to Tehran University of Medical Sciences. Due to necessity of HLA matching of hematopoietic stem cells derived from allogeneic umbilical cord (MNC) group we selected 150 cases of referred patients with our inclusion criteria and HLA analysis were done for these patients and then 36 cases of class 6 matched patients enrolled to the MNC group and 72 cases among the remaining patients randomly divided to mesenchymal stem cells derived from allogeneic umbilical cord (MSC) and control group . Therefore 108 cases enrolled in 3 divided groups of 36 patients.

Baseline clinical and neuroimaging evaluations were done for all of the 108 cases. Patients admitted in CMC and five million cell /kg of MNC and one million cell / kg of MHC stem cells that prepared in Royan Stem Cell Technology Co and Cell Tech Pharmed Co respectively were injected intrathecally with sedation. Only one dose of intrathecal injection was done for each participant .In the control group after insertion of the needle into the skin with an appearance of simulation of lumbar puncture no injection were done without the awareness of the patients or their parents. All of the participants admitted for observation and management of early side effects and discharged after 24 hours. Acute side effects and probable long term side effects will be reported and noted on our preformed questioners . Both participants and clinical evaluators are not aware of the 3 divided groups and our study is double blind.

Follow up clinical evaluators will be done at 1, 3, 6, and 12 months after injection for all of the participants .The intervention and control groups referred for neurorehabilitation with an identical protocol , that will be continued during the 12 months of follow up .

Standard brain Magnetic Resonance Imaging (MRI) with Magnetic Resonance Spectroscopy (MRS) and Diffusion Tensor Imaging (DTI) were done before injection and will be repeated after 12 months of clinical follow up.

For ethical consideration, we promised in the consent form that stem cell therapy will be done free of charge for participants of control group after 12 months of evaluation.

Inclusion criteria:

- Spastic cerebral palsy (Diparetic , Quadriparetic)
- Ages between 4 - 14 years
- Gross motor function classification (GMFC) between 2 -5
- No seizure disorder or with controlled seizures

- Evidence of definite acquired abnormal imaging findings compatible with Cerebral Palsy
- Informed consent is taken from their parents

Exclusion criteria:

- Normal brain MRI
- Progressive neurologic diseases
- Cortical malformations
- TORCH (Toxoplasmosis, Other, Rubella, Cytomegalovirus and Herpes Infections)
- Other types of cerebral palsy including athetoid , atonic , ataxic , and mixed type
- Acute intercurrent infections such as Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV) Malignancies
- Hemorrhagic diathesis
- Severe anemia (Hemoglobin less than 8 g/dl)
- Ventilator dependent pulmonary diseases
- Renal insufficiency
- Severe liver dysfunction

Primary outcome measures:

Different scoring systems such as Gross Motor Functional Classification System (GMFCS) , Gross Motor Function Measure Score (GMFM66) , Manual Ability Classification System (MACS) , Pediatric Evaluation of Disability Inventory (PEDI) , CP Quality of Life (QOL) , Life Habits Questionnaire and Modified Ashworth scale for spasticity were done at baseline and then will be repeated in follow ups until 12 months of final evaluation.

Change and Improvement to baseline of motor function with GMFCS score
Change and Improvement to baseline of motor function with Gross Motor Function Measure Score (GMFM66)
Change and Improvement to baseline of Manual Ability Classification System (MACS)
Change and Improvement to baseline of Pediatric Evaluation of Disability Inventory (PEDI).
Improvement of CP QOL
Improvement of Life Habits Questionnaire
Change and Improvement to baseline of Spasticity of patients according to Ashworth scale.
Improvement of developmental status according to Stanford Binet scale.

Secondary Outcome Measures:

Change and Improvement to baseline of Brain imaging findings according to MRI, MRS and DTI (baseline and at 12 months after injection)

Ethic Committee Approval:

Tehran University of Medical Sciences - 2017-06-06

Ethics committee Reference number: IR.TUMS.VCRREC.1996.2506.

Iranian Registry of Clinical Trials (IRCT) :

Trial Id No 7342 Registration date 2017-07-12 - IRCT201706176907N13

Sample size calculation:

To determine the sample size and attainment the maximum power, Sample size was calculated, based on the standard deviation reported from the study of Zali A,

et.al(($\sigma=10$) and Type I (α) error 0.05 and power 80% to achieve 12 score difference in mean of GMFC after intervention. The minimum number of patients required for this study was estimated 108 subjects, which are in each of the three groups MNC, MSC and Control 36 patient allocated, respectively.

Number of subjects N in each of two groups (Diggle *et al.*, 2002)

$$N = \frac{2(z_{\alpha} + z_{\beta})^2 (1 + (n - 1)\rho)}{n[(\mu_1 - \mu_2)/\sigma]^2}$$

- σ^2 is the assumed common variance in the two groups
- $\mu_1 - \mu_2$ is the difference in means of the two groups
- n is the number of timepoints
- ρ is the assumed correlation of the repeated measures



Randomization:

The patients are randomly allocated into three groups of intervention and control using a balanced block randomization technique. To do that, they were divided into blocks of 6 and 9. All subjects randomly allocated with online randomization software to generate random-number sequences. {Sealed Envelope Ltd. 2015.

Create a blocked randomization list. [Online] Available from:

<https://www.sealedenvelope.com/simple-randomiser/v1/lists> [Accessed 15 Dec 2015]}. Coordinator and Physician responsible for assessing inclusion / exclusion criteria and registering individuals are blind.

Due to necessity of HLA matching of hematopoietic stem cells derived from allogeneic umbilical cord (MNC) group we selected 150 cases of referred patients with our inclusion criteria and HLA analysis were done for these patients and then

36 cases of class 6 matched patients enrolled to the MNC group and 72 cases among the remaining patients randomly divided to mesenchymal stem cells derived from allogeneic umbilical cord (MSC) and control group . Therefore 108 cases enrolled in 3 divided groups of 36 patients.

Statistical analysis:

Intent-to-treat approach will be used to compare the mean GMFC as the initial outcome among the three groups. One-way analysis of variance will be used to investigate the difference between mean GMFC according to the study variables. Then, the post-hoc Scheffe test is used to determine the means differences. Moreover, backward stepwise multivariate linear regression will be used to evaluate the relationship between variables. The GEE model is used to evaluate the outcome changes over time. All analyses were performed at a significance level of 0.05 using the Stata 11 (StataCorp, College Station, TX, USA) statistical software.