TRAUMATIC BRAIN INJURY (TBI)

A. **Clinical Response**: Clinical response demonstrates an increase production of anti-inflammatory agents and formation of new blood vessels. Studies have shown an increase in the recovery of brain control over locomotor function after the transplantation of mesenchymal stem cells. In addition to physical examinations prior to stem cell graft and 6 months post-procedure, laboratory test results serve as evidence of repair process. Internationally recognized lab tests for monitoring traumatic brain injury (TBI) includes:
- Glasgow Coma Scale (GCS)
- Computerized Tomography (CT) Scans
- Magnetic Resonance Imaging (MRI)
- Intracranial Pressure Monitor

PRELIMINARIES

A. **Background**: Traumatic brain injury typically occurs when a sudden event causes damage to the brain. TBI can result from violent shock or an object penetrating the skull, which enters and/or affects the brain tissue. The symptoms of a TBI can vary from mild, moderate, to severe depending on the degree of damage to the brain. Mild TBI usually causes the affected person to remain conscious or experience loss of consciousness for a short period (seconds or minutes). Other symptoms related to mild TBI include headaches, confusion, lightheadedness, dizziness, fatigue, behavior or mood changes, and trouble with memory and concentration. A person with moderate to severe TBI may experience these same symptoms, but may also have headaches that do not get better over time, vomiting, nausea, convulsions or seizures, slurred speech, weakness or numbness in extremities, increased confusion, and restlessness.

B. **Treatment options**: Mild TBI usually requires no treatment other than resting and pain relievers to alleviate headaches.
- Surgery is done to patients with severe head-injuries to remove or repair hematomas or contusions.
- Medications to limit secondary damage after a brain injury include:
- Diuretics reduce the amount of fluid in tissues, therefore reducing the pressure inside the brain.
- Anti-seizure drugs are given during the first week after the injury to avoid additional brain damage.
- Coma inducing drugs are given to put patients in temporary comas in order to decrease the amount of oxygen delivered to the brain. Some brain injuries involve increased pressure in the cranial region, which does not allow blood vessels to deliver the right amount of oxygen and nutrients to brain cells. These drugs are administered to decrease the need of oxygen and nutrients and stabilize brain cells.

POTENTIAL BENEFITS OF STEM CELL TREATMENT

Mesenchymal Stem Cells (MSCs) found in several tissues, such as bone marrow and adipose tissue, have the capacity to produce growth and trophic factors in vivo and in vitro. In TBI patients with damaged brain cells, MSCs have facilitated the production of factors that activate the internal restorative mechanisms within the injured brain. Stem cell therapy studies have shown an increase in the anti-inflammatory cytokine production, which helps preserve the brain tissue. Additionally, studies have also revealed localization of MSCs in the region of injury. Intravenous administration of cells can increase level of neurotrophic growth factors such as NGF, BDNF, and bFGF. These growth factors have provided neuroprotective and beneficial effects in studies with brain injury. Mesenchymal stem cells have also shown the ability to restore cerebral blood flow by inducing the formation of new blood vessels.

TREATMENT & DELIVERY METHOD REQUIRED

A. Typical Recommended Treatment: Adipose Derived Stem Cells
B. Typical Delivery Method Required: Autologous Ad-SVF containing adult stem cells are infused in saline and injected via an intra-thecal injection in a volume of 3ml-5ml.
C. Recommended dosing: Recommended repeat dosing MSC’s every 6 to 8 weeks.
POTENTIAL RISKS OF STEM CELL INJECTION

There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of any results, excellent results can be attained. The medical team provides services in the most responsible, professional and diligent manner, always considering that procedures imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Low-grade fever
- Itching at injection site
- Allergic reaction
- Nerve/muscle injury
- Dizziness
- Swelling of joints
- Hot flashes
- Pain in joints
- Malaise
- Nausea
- Vascular spasm or obstruction
- Bruising
- Allergic reaction

Minor complications may include temporary arm or leg weakness, soreness at the injection site, the temporary increase in symptoms and spinal headache. Extremely rare complications can occur including infection, prolonged bleeding, and paralysis.

FREQUENTLY ASKED QUESTIONS

1. What are adult stem cells and how do they work?
They are undifferentiated cells found in tissues in the body, responsible for maintaining and repairing surrounding cells. These tissues include but are not limited to adipose tissue (fat tissue) and bone marrow. They have the ability to differentiate into various cell types, including neurons and also have the potential to activate the production of anti-inflammatory agents which makes adult stem cells a potential treatment to restore brain function in traumatic brain injuries. It has been proven that there are 500 times more stem cells stored in adipose tissue verse bone marrow, therefore, adipose derived stem cells are far superior.

The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

2. How can stem cell therapy help treat traumatic brain injury?
Traumatic brain injury, usually caused by an external force, affects brain function resulting in long-term complications. Mesenchymal stem cells have the potential to induce the formation of new blood vessels in the brain, increasing the blood flow to the affected area. The progenitor cells in the SVF have also demonstrated the ability to promote the production of growth factors and anti-inflammatory agents which show neuroprotective effects. Studies have shown an increase recovery of brain control over locomotor function after the transplantation of adult and mesenchymal stem cells.

3. How long do you think it would be before I see some improvement?
Stem cells therapy for traumatic brain injury is still an ongoing research topic and the results are not guaranteed. However, the response to the treatment varies from patient to patient. Studies have shown patients’ improvement 6-12 months after a stem cell therapy.

4. How will the stem cells be administered?
For traumatic brain injury isolated stem cells will be resuspended in 3ml to 5ml of saline and administered intrathecally.

5. Does smoking or drinking affect the therapy?
Smoking and the consumption of alcohol has been shown to be harmful to stem cells. We advise that people do not smoke or drink during their treatment, and it must absolutely be avoided the week following the treatment.

SUPPORTING ARTICLES

1. Intravenous transplantation of bone marrow mesenchymal stem cells promotes neural regeneration after traumatic brain injury
Authors: CFatemehAnbari, Mohammad Khalili, Ahmad Bahrami, ArezooKhoradmehr, FatemehSadeghian and FarzanehFesahat
Abstract:
To investigate the supplement of lost nerve cells in rats with traumatic brain injury by intravenous administration of allogenic bone marrow mesenchymal stem cells, this study established a Wistar rat model of traumatic brain injury by weight drop impact acceleration method and administered \(3 \times 10^6\) rat bone marrow mesenchymal stem cells via the lateral tail vein. At 14 days after cell transplantation, bone marrow mesenchymal stem cells differentiated into neurons and astrocytes in injured rat cerebral cortex and rat neurological function was improved significantly. These findings suggest that intravenously administered bone marrow mesenchymal stem cells can promote nerve cell regeneration in injured cerebral cortex, which supplement the lost nerve cells.
Neural Regeneration Research. 9.9 (May 1, 2014): p919.

2. Progenitor cell therapies as a novel treatment for traumatic brain injury: a pathway towards neuroprotection
Authors: Charles S Cox, Shinil K Shah and Peter A Walker
Abstract:
Traumatic brain injury (TBI) places a tremendous burden upon the American healthcare system and is associated with significant longterm patient morbidity [1]. In addition, all acute monotherapies focused on maintaining cerebral perfusion have failed to reverse the neuronal injury observed with TBI [2,3]. Preliminary research has shown potential neuroprotection after the intravenous injection of adult tissue progenitor or stem cells after TBI. By definition, adult tissue progenitor cells have the capacity for self-renewal and are multipotent (able to differentiate down multiple cell lines) [4]. Progenitor cells are maintained in select microenvironments throughout the body, which include bone marrow, adipose tissue, umbilical cord blood and within neural tissue (dentate gyrus and hippocampus). Within such niches, progenitor cell depletion, proliferation and activation are tightly regulated [5].
Therapy. 8.5 (Sept. 2011); p507.

3. Transplantation of Marrow Stromal Cells Restores Cerebral Blood Flow and Reduces Cerebral Atrophy in Rats with Traumatic Brain Injury: in vivo MRI Study
Authors: Lian Li, Quan Jiang, Chang Sheng Q, Guang Liang Ding, Qing Jiang Li, Shi Yang Wang, Ji Hyun Lee, Mei Lu, Asim Mahmood, Micheal Chopp
Abstract:
Cell therapy promotes brain remodeling and improves functional recovery after various central nervous system disorders, including traumatic brain injury (TBI). We tested the hypothesis that treatment of TBI with intravenous administration of human marrow stromal cells (hMSCs) provides therapeutic benefit in modifying hemodynamic and structural abnormalities, which are detectable by in vivo MRI. hMSCs were labeled with superparamagnetic iron oxide (SPION) nanoparticles. Male Wistar rats (300-350 g, n = 18) subjected to controlled cortical impact TBI were intravenously injected with 1 mL of saline (n = 9) or hMSCs in suspension (n = 9, approximately 3x 10^6 SPION-labeled hMSCs) 5 days post-TBI. In vivo MRI measurements consisting of cerebrospinal fluid flow (CBF), T2-weighted imaging, and 30 gradient echo imaging were performed for all animals 2 days post-TBI and weekly for 6 weeks. Functional outcome was evaluated with modified neurological severity score and Morris water maze test. Cell engraftment was detected in vivo by 30 MRI and confirmed by double staining.
JOURNAL OF NEUROTOXICITY. 28,535-545 (April 2011)

Blockade of Neuroglubin Reduces Protection of Conditioned Medium from Human Mesenchymal Stem Cells in Human Astrocyte Model (9T8G) Under a Scratch Assay.
Baez-Jurado E1, Vega GG1, Aliev G 2,3,4, Tarasov VV5, Esquinas P6, Echeverría V7, Barreto GE8,9.
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Abstract:
Previous studies have indicated that paracrine factors (conditioned medium) increase wound closure and reduce reactive oxygen species in a traumatic brain injury in vitro model. Although the beneficial effects of conditioned medium from human adipose tissue-derived mesenchymal stem cells (hMSCA-CM) have been previously suggested for various neurological diseases, their actions on astrocytic cells are not well understood. In this study, we have explored the effect of hMSCA-CM on human astrocyte model (T98G cells) subjected to scratch assay. Our results indicated that hMSCA-CM improved cell viability, reduced nuclear fragmentation, attenuated the production of reactive oxygen species, and preserved mitochondrial membrane potential and ultrastructural parameters. In addition, hMSCA-CM upregulated neuroglobin in T98G cells and the genetic silencing of this protein prevented the protective action of hMSCA-CM on damaged cells, suggesting that neuroglobin is mediating, at least in part, the protective effect of hMSCA-CM. Overall, this evidence suggests that the use of hMSCA-CM is a promising therapeutic strategy for the protection of astrocytic cells in central nervous system (CNS) pathologies.

KEYWORDS:
Adipose tissue; Astrocytes; Conditioned medium; Mesenchymal stem cells; Neuroglobin; Scratch assay

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