PARKINSON’S DISEASE (PD)

A. Clinical Response: Clinical response demonstrates a decrease in symptoms related to Parkinson's disease as well as regeneration of dopaminergic neurons (neurons involved in the secretion of dopamine). In addition to physical examinations prior to stem cell treatment and 6 months post-procedure, laboratory test and imaging results serve as evidence of repair process. Internationally recognized lab tests for monitoring Parkinson's disease include:
- Complete blood count (CBC) with differential
- Quantitative neurological exams
- EEG, MRI, CT scan or PET / SPECT scan of the brain
- Unified Parkinson's Disease Rating Scale

PRELIMINARIES

A. Background: Diabetes results from the insufficient production of insulin by the pancreas. This is caused by genetic predisposition as well as sometimes caused by destruction of pancreas by pancreatitis. Insulin allows glucose to enter the cells where it is converted to energy for metabolism. When there is an insulin deficiency, cells do not receive insulin and thus high blood sugar and high urine sugar occurs. The latter causes dehydration. Severe blood sugar is life threatening. Initially, the affected will have a large appetite which will diminish with time. As the disease advances and is not treated, lethargy, loss of appetite, vomiting, dehydration and ultimately coma will occur. Cataracts are a common occurrence and eventually all organs are affected. There are two types of Diabetes: Diabetes type 1 caused by a predisposition to the disease and Diabetes type 2 caused by a pre-existing condition which leads to diabetes [1].

Mostly older people are affected by this disease, but it may occur in younger adults. Parkinson's disease usually begins between the ages of 50 and 65, and it is slightly more common in men. Parkinson's disease presents with differing combinations of bradykinesia, rigidity, tremor, and loss of postural reflexes. There are many changes that may occur in the brain of people with Parkinson's such as the presence of Lewy bodies which are small clumps found within brain cells.

B. Causes of Parkinson’s Disease

The exact cause of Parkinson’s disease is still unknown, however there are several factors that may play a big role including:
- Genetics: Research has shown specific gene mutations that can potentially cause Parkinson's
- Environmental triggers: Exposure to certain toxins may increase the risk of developing Parkinson’s, however more research has to be done in order to identify these factors.
- Sex: Men being more likely to develop Parkinson’s Disease
- Age: Risk in developing Parkinson’s increases with age, usually beginning in the middle to late life.

C. Causes:

Treatment options: Parkinson's disease cannot be cured, however medication exist to help control the symptoms. These medication include, but are not limited to the following:
- Carbidopa-levodopa: Levodopa is a chemical that is dosed into the brain and is converted to dopamine. This medication is usually combined with carbidopa which prevents levopoda from converting to dopamine prematurely.
- Dopamine agonist: This chemical mimics dopamine effects on the brain.
- MAO-B inhibitors: They prevent the breakdown of dopamine in the brain by inhibiting MAO-B, which metabolizes dopamine.
- Deep brain stimulation: It is usually offered to people with advanced Parkinson's disease who are not responsive to medication.

POTENTIAL BENEFITS OF STEM CELL TREATMENT

Parkinson's disease is the second most common neurodegenerative disease which is characterized by the loss and degeneration of dopaminergic neurons (neurons involved in the secretion of dopamine). Mesenchymal stem cells, besides showing migration to the site of injury and having immunomodulatory and anti-inflammatory properties, have shown a capacity to protect and regenerate damaged dopaminergic neurons (Glavaski-Joksimovic & Bohn, 2013).
POTENTIAL BENEFITS OF STEM CELL TREATMENT

The production of diffusible trophic factor produced by mesenchymal stem cells supports the activation of neurogenesis as well as the integration of new neurons in a functional network (Cava, et al., 2011). A long term-clinical study has shown improvements in symptoms such as facial expression, gait and freezing episodes (Venkataramana, et al., 2010). Additionally, the transplantation of adipose derived stem cells has shown an improvement in behaviors such as tremor and motility (Chang, Lee, & Suh, 2014).

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 5-10 ml normal saline and injected intrathecally.
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 anes thesia, harvest ing 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 professional provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risk 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. Always, considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risk include but are not limited to:

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 and regenerated dopaminergic neurons making them a potential treatment for Parkinson’s disease. 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.

2. How can stem cell therapy help treat Parkinson’s disease?

Parkinson’s disease occurs when the neurons involved in the production of dopamine are dying causing the patient to lose the ability to regulate their movement, body and emotions. Stem cell therapy is designed to target these neurons. Mesenchymal stem cells may have protective and regenerative effects on dopaminergic neurons. They have also been shown to reduce Parkinson’s related complications such as tremors, freezing episodes, and rigidity.

3. How long do you think it would be before I see some improvement?

Stem cells therapy for Parkinson’s disease 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’ improvements as early as 3 months and 6-12 months after a stem cell therapy.
4. Are there any complications associated with this procedure?
Minimal bruising and soreness can be observed due to the liposuction procedure. This will normally last around 1-2 weeks, depending on the patient. Other complications have not been observed.

5. How will the stem cells be administered?
For Parkinson’s disease isolated stem cells will be administered intrathecally and sometime intravenously pending symptoms.

6. 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.

7. Will anyone follow up with me after the procedure?
A team member will follow up with you 1 day, 1 week, 3 months, 6 months and 1 year after the procedure. Follow ups help us evaluate the effectiveness of our treatment, and improve treatment protocols. We will be monitoring your progress closely. We are happy to address any issues or questions at anytime.

SUPPORTING ARTICLES


1. Mesenchymal stem cell therapy in Parkinson’s disease animal models.

Authors: 1IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, ContradaCasazza, 98124 Messina, Italy. 2IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, ContradaCasazza, 98124 Messina, Italy. Electronic address: emazzon.irccs@gmail.com.

Abstract: Parkinson’s disease is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, and as a consequence, by decreased dopamine levels in the striatum. Currently available therapies are not able to stop or reverse the progression of the disease. A novel therapeutic approach is based on cell therapy with stem cells, in order to replace degenerated neurons. Among stem cells, mesenchymal stem cells seemed the most promising thanks to their capacities to differentiate toward dopaminergic neurons and to release neurotrophic factors. Indeed, mesenchymal stem cells are able to produce different molecules with immunomodulatory, neuroprotective, angiogenic, chemotactic effects and that stimulate differentiation of resident stem cells. Mesenchymal stem cells were isolated for the first time from bone marrow, but can be collected also from adipose tissue, umbilical cord and other tissues. In this review, we focused our attention on mesenchymal stem cells derived from different sources and their application in Parkinson’s disease animal models.

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KEYWORDS: Adipose stem cells; Bone marrow stem cells; Mesenchymal stem cells; Parkinson’s disease; Umbilical cord stem cells
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2. Therapeutic Potential of Human Adipose-Derived Stem Cells in Neurological Disorders

Authors: Keun-A Chang, Jun-Ho Lee, Yoo-Hun Suh

Abstract: Stem cell therapy has been noted as a novel strategy to various diseases including neurological disorders such as Alzheimer’s disease, Parkinson’s disease, stroke, amyotrophic lateral sclerosis, and Huntington’s disease that have no effective treatment available to date. The adipose-derived stem cells (ASCs), mesenchymal stem cells (MSCs) isolated from adipose tissue, are well known for their pluripotency with the ability to differentiate into various types of cells and immuno-modulatory property. These biological features make ASCs a promising source for regenerative cell therapy in neurological disorders. Here we discuss the recent progress of regenerative therapies in various neurological disorders utilizing ASCs.


3. Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson’s disease
**Authors:** Neelam k.Venkatararamana, Satish K.V.Kumar, Sudheer Balaraju, Radhika Chemmangattu Radhakrishnan, Abhilash Bansal, Ashish Dixit, Deepthi K. RAO, Madhulita Das, Majahar Jan, Pawan Kumar Gipta, and Satish M. Totey

**Abstract:** Parkinson's disease (PD) is a progressive neurodegenerative disease for which stemcell research has created hope in the last few years. Seven PD patients aged 22 to 62 years with a mean duration of disease 14.7 ± 7.56 years were enrolled to participate in the prospective, uncontrolled, pilot study of single-dose, unilateral transplantation of autologous bone-marrow-derived mesenchymal stem cells (BM-MSCs). The BM-MSCs were transplanted into the sublateral ventricular zone by stereotaxic surgery. Patients were followed up for a period that ranged from 10 to 36 months. The mean baseline “off” score was 65 ±22.06, and the mean baseline “on” score was 50.6 ±15.85. Three of 7 patients have shown a steady improvement in their “off”/“on” Unified Parkinson's Disease Rating Scale (UPDRS). The mean “off” score at their last follow-up was 43.3 with an improvement of 22.9% from the baseline. The mean “on” score at their last follow-up was 31.7, with an improvement of 38%. Hoehn and Yahr (H&Y) and Schwab and England (S&E) scores showed similar improvements from 2.7 and 2.5 in H&Y and 14% in S&E scores, respectively. A subjective improvement was found in symptoms like facial expression, gait, and freezing episodes. 2 patients have significantly reduced the dosages of PD medicine. These results indicate that our protocol seems to be safe, and no serious adverse events occurred after stem-cell transplantation in PD patients. The number of patients recruited and the uncontrolled nature of the trial did not permit demonstration of effectiveness of the treatment involved. However, the results encourage future trials with more patients to demonstrate efficacy. (Translational Research 2010;155:62–70)

**4. Multiple neurogenic and neurorescue effects of human mesenchymal stem cell after transplantation in anexperimental model of Parkinson’s disease**

**Authors:** Lidia Cova, Marie-ThereseArmentero, Eleonora Zennaro, CinziaCalzarossa, PatriziaBossolasco, Giuseppe Busca, Giorgio LambertenghiDelliliers, Elio Polli, Giuseppe Nappi, VincenzoSilani, Fabio Blandini

**Abstract:** Stimulation of endogenous repair in neurodegenerative diseases, such as Parkinson’s disease (PD), appears to be a novel and promising therapeutic application of stem cells (SCs). In fact SCs could propel local microenvironmental signals to sustain active endeavors for damaged neurons substitution, normally failing in non-supportive pathological surroundings. In this study, we demonstrated that two different doses of naïve human adult mesenchymal stem cells (hMSCs), implanted in the striatum of rats lesioned with 6-hydroxydopamine (6-OHDA), positively survived 23 days after transplantation. Their fate was directly influenced by the surrounding host environment while grafted hMSCs, dose dependently, regionally sustained the survival of striatal/nigral dopaminergic terminals and enhanced neurogenesis in the Subventricular Zone (SVZ). The number of proliferative cells (Ki67/Proliferating Cell Nuclear Antigen +) as well as neuroblasts migration significantly augmented in the lesioned striatum of transplanted animals compared to controls. No SVZ astrogenesis was detected in all experimental conditions, irrespectively of graft presence. Activation of endogenous stem cell compartments and rescue of dopaminergic neurons, supported by the persistent release of specific cytokine by MSCs in vivo, appeared in principle able to contrast the neurodegenerative processes induced by the 6-OHDA lesion. Our results suggest that reciprocal influences between grafted cells and endogenous neural precursors could be important for the observed neurorescue effect on several brain regions. Altogether, our data provide remarkable cues regarding the potential of hMSCs in promoting endogenous reparative mechanisms that may prove applicable and beneficial for PD treatment.

**5. Mesenchymal stem cells and neuroregeneration in Parkinson’s disease**

**Authors:** Aleksandra Glavaski-Joksimovic, Martha C. Bohn

**Abstract:** Parkinson’s disease (PD) is a prevalent neurodegenerative disorder characterized by a progressive and extensive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and their terminals in the striatum, which results in debilitating movement disorders. This devastating disease affects over 1 million individuals in the United States and is increasing in incidence worldwide. Currently available pharmacological and surgical therapies ameliorate clinical symptoms in the early stages of disease, but they are not stop or reverse degeneration of DA neurons. Stem cell therapies have come to the forefront of the PD research field as promising regenerative therapies. The majority of preclinical stem cell studies in experimental models of PD are focused on the idea that stem-cell-derived DA neurons could be developed for replacement of diseased neurons. Alternatively, our studies and the studies from other groups suggest that stem cells also have the potential to protect and stimulate regeneration of compromised DA neurons. This review is focused on strategies based on the therapeutic potential for PD of the neurotrophic and neuroregenerative properties of a subclass of stem cells, mesenchymal stem cells (MSCs).

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