PARKINSON'S DISEASE (PD)

1. PARKINSON'S DISEASE (PD) PROTOCOL

A. Clinical Response: Clinical response demonstrates a decrease in progression of disease and evidence of an improved repair process. In addition to physical examinations prior to stem cell graft 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

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with Parkinson's Disease. The endovascular/intravenous Ad-SVF Containing Adult Stem Cell Procedure should serve to compliment the patient's current treatment regimen or to promote healing when current treatment is not responding.

2. PRELIMINARIES

A. Parkinson's Disease is a chronic, degenerative movement disorder, affecting the basal ganglia. Parkinson's disease presents with differing combinations of bradykinesia, rigidity, tremor and loss of postural reflexes

B. Causes of Parkinson's Disease:

- ***Genetic Susceptibility***
- ***Environmental Factors***

C. Treatment options: The goal of medical management of Parkinson disease is to provide control of signs and symptoms for as long as possible while minimizing adverse effects.

- ***L-dopa*** combined with a peripheral-acting dopa-decarboxylase inhibitor provides the mainstay of treatment in Parkinson's disease. The initiation of L-dopa therapy should be delayed until there is significant disability, since there is concern regarding long-term side-effects.
- ***Other pharmacological treatments*** include anticholinergic drugs, dopamine receptor agonists, selegiline and amantadine.
- **Surgery:** Stereotactic thalamotomy can be used to treat tremor, though this is relatively infrequently needed because of the medical treatments available.

The treatments described in this manual are considered experimental and have not been evaluated or approved by the FDA.

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician revises the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

- ***Pre-op Evaluation / post-op medical consultation***: A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment. On the morning prior to procedure history and physical are performed by physician.

- ***Harvesting of adipose tissue***: Adipose tissue acquisition can be summarized as three step process:

  - ***Application of anesthetic / injection of tumescent solution***

  - ***Waiting time***

  - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. A tissue sample is then obtained using 60 cc syringe(s) to aspirate 50 to 100 cc of adipose tissue. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

- **Autologous implant of Ad-SVF:** The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion, intrathecal injection, or through the carotid artery.

B. Post-op care for PD procedure:

- Patient remains under routine hospital care for 4 to 6 hours post-op
- Post-op evaluation before discharge and 24 hours post-op
- Patient maintains pressure dressing for 24 hours post-op
- 500 mg Ciprofloxacin PO bid for 7 days

C. Risks: 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 perfect results, excellent results can be attained. The surgeon 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 risks include but are not limited to:

- Vascular spasm
- Vascular obstruction
- Pseudo-aneurysms
- Lymphadenopathy
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Low-grade fever
- Hot Flashes
- Dizziness
- Nausea / Vomiting
- Headache
- Allergic reaction
- Pain at site of injections
- Bleeding at injection site
- Itching at injection site
- Malaise

D. Benefits: Adipose derived stem cells have the potential to repair nerve tissue. These stem cells also have immune modulating abilities. Adult stem cells possess the ability to repair damaged cells leading to tissue regeneration and ultimately promoting the healing process.

E. Follow-up Plan: Clinical response demonstrates a decrease of disease and improvement of symptoms associated with Parkinson's disease. Review of changes to internationally recognized lab results. Standards for follow-up:

- ***Pre-Ad-SVF implant***: Clinical evaluation of PD symptoms. Review & record current laboratory and or imaging results specific to PD.

- ***3 months after Ad-SVF implant***: Clinical evaluation of PD symptoms. Review & record current laboratory and imaging results specific to PD.

- ***6 months after Ad-SVF implant***: Clinical evaluation of PD symptoms, physical exam, and neurological assessment. Review & record current laboratory, imaging.

PD – Adult Stem Cells Schedule of Events

1. **Initial Patient Evaluation:** A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

   A. Pre-Examination:
   - You will have a physical exam, which will include measuring your blood pressure, temperature and heart rate (vital signs).
   - Your doctor will discuss your medical history and any medications that you are taking.
   - Your doctor will assess how well you can perform your daily activities
   - If needed, you will have a urine or blood pregnancy test.
   - Blood will be taken.

   B. Additional Tests: should be done during or soon after this visit
   - Complete blood count (CBC) with differential
   - Quantitative neurological exams
   - EEG, MRI, CT scan or PET / SPECT scan of the brain

   C. Review Results: After your doctor has reviewed the results of these tests, he or she will assess whether you are a good candidate for stem cell therapy. If you decide to obtain this therapy you will sign a consent form. A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

1. **Pre-Operation / Stem Cell Procedure:**

   A. Two Weeks Before Procedure:

   - No Aspirin or medicines that contain aspirin or Ibuprofen since it interferes with normal blood clotting. You may take Tylenol or generic forms of this drug.
   - Discuss with your primary physician to discontinue anticoagulant drugs at least 1 week before the procedure.
   - Please discontinue all herbal medications as many have side effects that could complicate a surgical procedure by inhibiting blood clotting, affecting blood pressure, or interfering with anesthetics.
   - Please discontinue all diet pills whether prescription, over-the-counter or herbal.
   - NO SMOKING because nicotine reduces blood flow to the skin and can cause significant complications during healing.
   - Purchase a compressive garment to wear after the lipoaspiration procedure.

B. Morning of the Procedure:

- Have a light breakfast.
- Take your regular prescribed medications
- Wear comfortable, loose-fitting clothes that do not have to be put on over your head.

2. Stem Cell Procedure:

A. Preparation & Harvesting of Adipose Tissue:

- ***Application of anesthetic / injection of tumescent solution***
- ***Waiting time (~15 – 20 minutes)***
- ***Acquisition of blood sample***
- ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.
- **Autologous implant of Ad-SVF:** The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion, intrathecal injection, or through the carotid artery.

3. Recommended Post-Operation / Stem Cell Therapy Schedule:

A. Post-Op Medical Instruction - **(Please follow these instructions closely!)**

- Patient remains under routine hospital care for 4 to 6 hours post-op
- Post-op evaluation before discharge and 24 hours post-op
- Patient maintains pressure dressing for 24 hours post-op
- 500 mg Ciprofloxacin PO bid for 7 days
- ***Post-op medication*** will be given to you the day of your surgery. They will consist of an antibiotic and a painkiller:
  - *Antibiotic*: Cephalexin/Cipro, please take as directed beginning the day after surgery
  - *Painkiller:* Please take as directed and only as needed for pain

  * If you are unable to take any of these medications, please contact your patient coordinator so we can arrange for other medications.
- ***Resume previous medication*** as directed by the physician
- ***Report any symptoms of feeling unwell***: fever, pain, etc. Patients should be seen promptly by an ophthalmologist for full evaluation should any of the above symptoms be encountered.

- It is recommended that the ***patient have a companion stay with him or her*** for at least 24 hours after discharge.
- You should ***expect some of blood-tinged anesthetic solution to drain from the incision sites*** during the first 24 to 48 hours. This will vary from patient to patient. Maxi-pads are recommended for bandages over your incision sites. You may take a shower 24 hours after the procedure.
- ***Compressive garments should be worn*** 24 hours a day for the first week and 12 hours a day for the second week.
- ***Do not shower for the first 24 hours***. ***Do not submerge yourself in any water*** (i.e. taking a bath or swimming) for the 1st week.
- ***If you experience nausea or vomiting it is probably due to the medication***. Please try to take it with food. If it persists, please contact our office.
- ***Diet-meals are not restricted.***
- ***Drink plenty of clear fluids***. We recommend 8 glasses of water or fruit juice every day.
- ***Do not drink any alcohol*** for 48 hours and limit alcohol intake for the first week.

B. <u>Post-Op Medical Consultation Schedule: 3 months & 6 months</u>

- Review of medical history
- Review of medication history
- Review of any adverse events since the previous visit
- Clinical evaluation of PD symptoms
- Review & record current laboratory and imaging results

Your doctor will contact you by phone within the first week to follow up then future follow up visits will be arranged through your patient coordinator. If you need assistance before do not hesitate to contact us.

Parkinson's Disease – Supporting Studies

Parkinsonism Relat Disord. 2014 Jan;20 Suppl 1:S128-31. doi: 10.1016/S1353-8020(13)70031-2.

The promises of stem cells: stem cell therapy for movement disorders.

Mochizuki H, Choong CJ, Yasuda T.
Author information
Abstract

Despite the multitude of intensive research, the exact pathophysiological mechanisms underlying movement disorders including Parkinson's disease, multiple system atrophy and Huntington's disease remain more or less elusive. Treatments to halt these disease progressions are currently unavailable. With the recent induced pluripotent stem cells breakthrough and accomplishment, stem cell research, as the vast majority of scientists agree, holds great promise for relieving and treating debilitating movement disorders. As stem cells are the precursors of all cells in the human body, an understanding of the molecular mechanisms that govern how they develop and work would provide us many fundamental insights into human biology of health and disease. Moreover, stem-cell-derived neurons may be a renewable source of replacement cells for damaged neurons in movement disorders. While stem cells show potential for regenerative medicine, their use as tools for research and drug testing is thought to have more immediate impact. The use of stem-cell-based drug screening technology could be a big boost in drug discovery for these movement disorders. Particular attention should also be given to the involvement of neural stem cells in adult neurogenesis so as to encourage its development as a therapeutic option.

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KEYWORDS:

Induced pluripotent stem cell, Movement disorders, Parkinson's disease, Stem cell

PMID: 24262163 [PubMed - in process]

Parkinson's Disease – Supporting Studies

BMC Cell Biol. 2012 Aug 7;13:21. doi: 10.1186/1471-2121-13-21.

Human adipose tissue-derived multilineage progenitor cells exposed to oxidative stress induce neurite outgrowth in PC12 cells through p38 MAPK signaling.

Moriyama M, Moriyama H, Ueda A, Nishibata Y, Okura H, Ichinose A, Matsuyama A, Hayakawa T.
Author information

Abstract

BACKGROUND:

Adipose tissues contain populations of pluripotent mesenchymal stem cells that also secrete various cytokines and growth factors to support repair of damaged tissues. In this study, we examined the role of oxidative stress on human adipose-derived multilineage progenitor cells (hADMPCs) in neurite outgrowth in cells of the rat pheochromocytoma cell line (PC12).

RESULTS:

We found that glutathione depletion in hADMPCs, caused by treatment with buthionine sulfoximine (BSO), resulted in the promotion of neurite outgrowth in PC12 cells through upregulation of bone morphogenetic protein 2 (BMP2) and fibroblast growth factor 2 (FGF2) transcription in, and secretion from, hADMPCs. Addition of N-acetylcysteine, a precursor of the intracellular antioxidant glutathione, suppressed the BSO-mediated upregulation of BMP2 and FGF2. Moreover, BSO treatment caused phosphorylation of p38 MAPK in hADMPCs. Inhibition of p38 MAPK was sufficient to suppress BMP2 and FGF2 expression, while this expression was significantly upregulated by overexpression of a constitutively active form of MKK6, which is an upstream molecule from p38 MAPK.

CONCLUSIONS:

Our results clearly suggest that glutathione depletion, followed by accumulation of reactive oxygen species, stimulates the activation of p38 MAPK and subsequent expression of BMP2 and FGF2 in hADMPCs. Thus, transplantation of hADMPCs into neurodegenerative lesions such as stroke and Parkinson's disease, in which the transplanted hADMPCs are exposed to oxidative stress, can be the basis for simple and safe therapies.

PMID: 22870983 [PubMed - indexed for MEDLINE] PMCID: PMC3465210

The treatments described in this manual are considered experimental and have not been evaluated or approved by the FDA.

Parkinson's Disease – Supporting Studies

J Neurosci Res. 2013 Jan;91(1):62-72. doi: 10.1002/jnr.23128. Epub 2012 Oct 17.

Therapeutic effects of human mesenchymal and hematopoietic stem cells on rotenone-treated parkinsonian mice.

Inden M, Takata K, Nishimura K, Kitamura Y, Ashihara E, Yoshimoto K, Ariga H, Honmou O, Shimohama S. Author information

Abstract

To appreciate the potential applications of stem cell technology in neurodegenerative diseases, including Parkinson's disease (PD), it is important to understand the characteristics of the various types of stem cells. In this study, we designed a set of experiments to compare the ability of three types of human stem cells--mesenchymal stem cells (MSCs), bone marrow CD34(+) cells (BM), and cord blood CD34(+) cells (CB)--using rotenone-treated NOD/SCID mice. Rotenone was orally administered once daily at a dose of 30 mg/kg for 56 days to induce a parkinsonian phenotype. Intravenous delivery of CB into rotenone-treated mice was slightly more beneficial than that of MSCs or BM according to both histological and behavioral analyses. Human nucleus (hNu)(+) cells, which are a specific marker of human cells, were observed in the striatum of rotenone-treated mice transplanted with stem cells. These hNu(+) cells expressed tyrosine hydroxylase (TH). Additionally, α-synuclein(+)/TH(+) cells in the substantia nigra pars compacta decreased significantly following stem cell transplantation. Immunohistochemical analysis also revealed that chronic exposure to rotenone decreased glial cell line-derived neurotrophic factor immunoreactivity and that the reduction was improved by each stem cell transplantation. Gene expression analyses revealed that MSCs, BM, and CB expressed several neurotrophic factors. These results suggest that the beneficial effects of intravenous delivery of stem cells into rotenone-treated mice may result not only from a neurotrophic effect but also from endogenous brain repair mechanisms and the potential of intravenous delivery of stem cells derived from an autologous source for clinical applications in PD.

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Parkinson's Disease – References

Inden, M., Takata, K., Nishimura, K., Kitamura, Y., Ashihara, E., Yoshimoto, K., Ariga, H., Honmou, O. and Shimohama, S. (2013), Therapeutic effects of human mesenchymal and hematopoietic stem cells on rotenone-treated parkinsonian mice. J. Neurosci. Res., 91: 62–72. doi: 10.1002/jnr.23128

Mochizuki H, Choong CJ, Yasuda T. (2013), The promises of stem cells: stem cell therapy for movement disorders. Elsevier Ltd. 20 Suppl 1:S128-31. doi: 10.1016/S1353-8020(13)70031-2.

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