SPINAL CORD INJURIES

1. SPINAL CORD INJURIES PROTOCOL

A. Clinical Response: Patients may experience improvements in function and quality of life parameters. This could include improvements as measured by:

- Review of Medical History
- Review of Medication History
- Complete physical exam (including vital signs of sitting blood pressure, temperature, and heart rate)
- Serum or urine pregnancy test (for women of childbearing age)
- Frankel Score
- ASIA Scale
- Manual Muscle Test

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with spinal cord injuries 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. Background: Spinal Cord Injuries (SCI) are caused by trauma to the spinal cord that impairs physical function, mobility or feeling. The majority of patients suffering from SCI have an intact spinal cord, but still have enough cellular damage to result in a loss of physical functioning. The effects caused by SCI depend heavily on the type of injury and the level of injury. A spinal cord injury refers to any injury to the spinal cord that is caused by trauma. Spinal cord injuries often cause changes in strength, body function and movement. Spinal cord injuries can be described as various levels of incomplete, where complete means total loss of function. Recent studies have focused on the use of adult stem cells for spinal cord injury patients. It has been discovered that introduction of mesenchymal stem cells either intralesionally or intravenously can be successful in improving functional recovery in chronic spinal cord injuries [1]. There are two types of SCI injuries:

- ***Complete***: A complete injury means that there is no function below the level of the injury; no sensation and no voluntary movement. Both sides of the body are equally affected.
- ***Incomplete:*** An incomplete injury means that there is some functioning below the primary level of the injury. A person with an incomplete injury may be able to move one limb more than another, may be able to feel parts of the body that cannot be moved, or may have more functioning on one side of the body than the other. With incomplete injuries there will be some variation in these prognoses.

B. Causes of Spinal Cord Injuries:

- ***Trauma***: a car accident, work accident, gunshot, fall, assault, sports injury, etc

- ***Disease:*** Transverse Myelitis, Polio, Spina Bifida (disease causing incomplete development of the brain & spinal cord), Friedreich's Ataxia, etc

C. Treatment Options:

- ***Medications***: Methylprednisolone (Medrol) is a treatment option for an acute spinal cord injury. Methylprednisolone helps by reducing damage to nerve cells and decreasing inflammation near the site of injury.
- ***Immobilization***: Traction can help bring the spine into proper alignment.
- ***Surgery***: Surgery helps to remove fragments of bones, foreign objects, herniated disks or fractured vertebrae that appear to be compressing the spine. Surgery may also be needed to stabilize the spine to prevent future pain or deformity.

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***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.

- ***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.

- ***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 locally by intrathecal or intravenous delivery of cells.

B. 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:

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

C. Benefits: Adipose stem cell therapy utilizes regenerative stem cells to repair cellular damage that was caused from spinal cord injuries. Stem cell therapy helps control inflammation and promotes regeneration that may improve a SCI patient's ability to move and feel.

D. Follow-up plan:

- ***3 months after Ad-SVF implant***: Clinical evaluation of spinal cord injury based on the Frankel Score and the ASIA Scale. Review & record current laboratory determinations.

- ***6 months after Ad-SVF implant***: Clinical evaluation of spinal cord injury based on the Frankel Score, ASIA Scale and Manual Muscle Test. Review & record current laboratory determinations.

Spinal Cord – Adult Stem Cells Schedule of Events

	Baseline Evaluation and Data Review	Study Intervention	Three-month Follow-up	Six-month Follow-up
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*
Informed Consent	X	X		
Adverse Event Review/Status	X	X	X	X
Medical History Review	X	X	X	X
Medication History Review	X	X	X	X
Physical examination including vital signs	X	X	X	X
Pregnancy test[1]	X	X		
Laboratory determinations	X	X	X	X
Frankel Score	X		X	X
ASIA Scale	X		X	X
Manual Muscle Test	X			X
Liposuction and ASC isolation		X		
Adipose-derived stem cell implantation		X		

[1] For female patients of childbearing age.

Spinal Cord – 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

   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.

2. **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.

3. Stem Cell Procedure:

A. Preparation & Harvesting of Adipose Tissue:

- ***Application of anesthetic / injection of tumescent solution***
- ***Waiting time (~15 – 20 minutes)***
- ***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.

B. Autologous implant of Ad-SVF: To do the implant procedure, the cells are directly injected intra-articularly into the affected joint(s). You will be closely monitored throughout the procedure.

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

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

- ***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***: dizziness, changes in heart rate, pain, or fever. Patients should be seen promptly by an physician 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. Post-Op Medical Consultation Schedule:

- Patient Status
- Review of Medical History
- Review of Medication History

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.

Frankel Score

Grade	Description
Grade A	Complete neurological injury – no motor or sensory function clinically detected below the level of injury
Grade B	Preserved sensation only – no motor function clinically detected below the level of injury; sensory function remains below the level of injury, but may include only partial function (sacral sparing qualifies as preserved sensation)
Grade C	Preserved motor non-functional – some motor function observed below the level of the injury, but is no practical use to the patient.
Grade D	Preserved motor function – useful motor function below the level of the injury patient can move lower limbs and walk with or without aid, but does not have a normal gait or strength in all motor groups.
Grade E	Normal motor – no clinically detected abnormality in motor or sensory function with normal sphincter function; abnormal reflexes and subjective sensory abnormalities may be present.

Spinal Cord – Supporting Studies

J Neurol Sci. 2009 Oct 15;285(1-2):67-77. doi: 10.1016/j.jns.2009.05.027. Epub 2009 Jun 24.

A comparison of autologous and allogenic bone marrow-derived mesenchymal stem cell transplantation in canine spinal cord injury.

Jung DI, Ha J, Kang BT, Kim JW, Quan FS, Lee JH, Woo EJ, Park HM.

Abstract

The purpose of this study is to compare the therapeutic effects between autologous and allogenic bone-marrow-derived mesenchymal stem cell (MSC) transplantation in experimentally-induced spinal cord injury (SCI) of dogs. Thirty adult Beagle dogs (control group=10, autologous group=10, and allogenic group=10) were used in this study. Prelabeled MSCs were intrathecally transplanted through the lumbar spinal cord into the injured lesion at a density of 1 x 10(7) cells 7 days after SCI. Neurological signs of dogs in both autologous and allogenic groups were improved in their pelvic limbs after SCI compared with those in control group. Both autologous and allogenic groups showed significantly higher the Olby scores than control group ($p<0.05$). This finding was consistent with results of MRI and histopathological examination in both groups. Immunofluorescence analysis revealed that prelabeled autologous and allogenic MSCs were detected in the injured lesions both at 1 and 4 weeks after transplantation. However, the distribution ratio of MSCs on the injured lesion in allogenic group was significantly decreased at 4 weeks after transplantation relatively to at 1 week after transplantation. The mRNA expression for neurotrophic factors in both allogenic and autologous groups was significantly higher than that in control groups ($p<0.05$). Even though autologous MSC transplantation showed more beneficial effect than that of allogenic MSC transplantation, transplantation of allogenic MSCs also improved functional recovery following SCI. This study demonstrates that both autologous and allogenic MSC transplantation could be clinically useful therapeutic approaches for treating SCI.

PMID: 19555980 [PubMed - indexed for MEDLINE]

Spinal Cord – Supporting Studies

Stem Cells Int. 2012;2012:921053. doi: 10.1155/2012/921053. Epub 2012 Mar 4.

Mesenchymal stem cell for prevention and management of intervertebral disc degeneration.

Longo UG, Papapietro N, Petrillo S, Franceschetti E, Maffulli N, Denaro V.

Abstract
Intervertebral disc degeneration (IVD) is a frequent pathological condition. Conservative management often fails, and patients with IVD degeneration may require surgical intervention. Several treatment strategies have been proposed, although only surgical discectomy and arthrodesis have been proved to be predictably effective. The aim of biological strategies is to prevent and manage IVD degeneration, improve the function, the anabolic and reparative capabilities of the nucleus pulposus and annulus fibrosus cells, and inhibit matrix degradation. At present, clinical applications are still in their infancy. Further studies are required to clarify the role of mesenchymal stem cells and gene therapy for the prevention and treatment of IVD degeneration.

PMID: 22550520 [PubMed] PMCID: PMC3328194

Spinal Cord – Supporting Studies

Cytotherapy. 2013 Apr;15(4):434-48. doi: 10.1016/j.jcyt.2012.11.015. Epub 2013 Feb 1.

Comparison of mesenchymal stromal cells from human bone marrow and adipose tissue for the treatment of spinal cord injury.

Zhou Z, Chen Y, Zhang H, Min S, Yu B, He B, Jin A.

Abstract

BACKGROUND:

Bone marrow and subcutaneous adipose tissue are both considered prospective sources of mesenchymal stromal cells (MSCs), which can be used in cell therapy for spinal cord injury (SCI). The present study investigated whether human adipose tissue-derived mesenchymal stromal cells (hADSCs) transplanted into a rat model of SCI would lead to similar or improved neurologic effects compared with human bone marrow-derived mesenchymal stromal cells (hBMSCs).

METHODS:

hADSCs and hBMSCs were isolated from five adult donors. These MSCs were characterized using flow cytometry, immunocytochemistry, real-time polymerase chain reaction and enzyme-linked immunosorbent assay. Immediately after SCI, 2 × 10(5) hBMSCs or hADSCs were injected into the injured spinal cord. Locomotor function, cell survival and differentiation, spinal cord tissue morphology and brain-derived neurotrophic factor (BDNF) expression were compared between groups.

RESULTS:

hADSCs and hBMSCs showed similar surface protein expression, and hADSCs showed higher proliferative activity with higher expression of vascular endothelial cell growth factor, hepatocyte growth factor and BDNF than hBMSCs. After transplant, both hADSCs and hBMSCs migrated within the injured spinal cord without differentiating into glial or neuronal elements. Administration of hADSCs was associated with marked changes in the SCI environment, with significant increases in BDNF levels. This was simultaneously associated with increased angiogenesis, preserved axons, decreased numbers of ED1-positive macrophages and reduced lesion cavity formation. These changes were accompanied by improved functional recovery.

CONCLUSIONS:

The present results suggest that hADSCs would be more appropriate for transplant to treat SCI than hBMSCs.

Spinal Cord – Supporting Studies

Cell Mol Life Sci. 2013 Oct;70(20):3871-82. doi: 10.1007/s00018-013-1290-8. Epub 2013 Mar 1.

Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration?

Teixeira FG, Carvalho MM, Sousa N, Salgado AJ.

Abstract

The low regeneration potential of the central nervous system (CNS) represents a challenge for the development of new therapeutic strategies. Mesenchymal stem cells (MSCs) have been proposed as a possible therapeutic tool for CNS disorders. In addition to their differentiation potential, it is well accepted nowadays that their beneficial actions can also be mediated by their secretome. Indeed, it was already demonstrated, both in vitro and in vivo, that MSCs are able to secrete a broad range of neuroregulatory factors that promote an increase in neurogenesis, inhibition of apoptosis and glial scar formation, immunomodulation, angiogenesis, neuronal and glial cell survival, as well as relevant neuroprotective actions on different pathophysiological contexts. Considering their protective action in lesioned sites, MSCs' secretome might also improve the integration of local progenitor cells in neuroregeneration processes, opening a door for their future use as therapeutical strategies in human clinical trials. Thus, in this review we analyze the current understanding of MSCs secretome as a new paradigm for the treatment of CNS neurodegenerative diseases.

PMID: 23456256 [PubMed - indexed for MEDLINE]

Spinal Cord – Supporting Studies

Adv Exp Med Biol. 2012;760:53-73.

Stem cells and spinal cord injury repair.

Karimi-Abdolrezaee S, Eftekharpour E.

Abstract
Spinal cord injury (SCI) has remained a challenging area for scientists and clinicians due to the adverse and complex nature of its pathobiology. To date, clinical therapies for debilitating SCI are largely ineffective. However, emerging research evidence suggests that repair of SCI can be promoted by stem cell-based therapies in regenerative medicine. Over the past decade, therapeutic potential of different types of stem cells for the treatment of SCI have been investigated in preclinical models. These studies have revealed multiple beneficial roles by which stem cells can improve the outcomes of SCI. This chapter will summarize the recent advances in the application of stem cells in regenerative medicine for the repair of SCI.

PMID: 23281513 [PubMed - indexed for MEDLINE]

Spinal Cord – Supporting Studies

Stem Cells Dev. 2011 Aug;20(8):1297-308. doi: 10.1089/scd.2010.0466. Epub 2011 Mar 17.

Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans.

Ra JC, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, Kim YJ, Jo JY, Yoon EJ, Choi HJ, Kwon E.
Author information

Abstract
Adipose tissue-derived mesenchymal stem cells (AdMSCs) represent an attractive and ethical cell source for stem cell therapy. With the recent demonstration of MSC homing properties, intravenous applications of MSCs to cell-damaged diseases have increased. In the present study, the toxicity and tumorigenicity of human AdMSCs (hAdMSCs) were investigated for clinical application. Culture-expanded hAdMSCs showed the typical appearance, immunophenotype, and differentiation capacity of MSCs, and were genetically stable at least 12 passages in culture. Cells suspended in physiological saline maintained their MSC properties in a cold storage condition for at least 3 days. To test the toxicity of hAdMSCs, different doses of hAdMSCs were injected intravenously into immunodeficient mice, and the mice were observed for 13 weeks. Even at the highest cell dose (2.5×10(8) cells/kg body weight), the SCID mice were viable and had no side effects. A tumorigenicity test was performed in Balb/c-nu nude mice for 26 weeks. Even at the highest cell dose (2×10(8) MSCs/kg), no evidence of tumor development was found. In a human clinical trial, 8 male patients who had suffered a spinal cord injury >12 months previous were intravenously administered autologous hAdMSCs (4×10(8) cells) one time. None of the patients developed any serious adverse events related to hAdMSC transplantation during the 3-month follow-up. In conclusion, the systemic transplantation of hAdMSCs appears to be safe and does not induce tumor development.

Spinal Cord – References

[1] Kim JW, Ha KY, Molon JN, Kim YH. Spine (Phila Pa 1976). 2013 Apr 26. Bone Marrow Derived Mesenchymal Stem Cell Transplantation for Chronic Spinal Cord Injury in Rats: Comparative Study Between Intralesional and Intravenous Transplantation.

Jung DI, Ha J, Kang BT, Kim JW, Quan FS, Lee JH, Woo EJ, Park HM. A comparison of autologous and allogenic bone marrow-derived mesenchymal stem cell transplantation in canine spinal cord injury. (2009). J Neurol Sci. doi: 10.1016