1. SPINAL CORD INJURIES

A. Clinical Response: Clinical response demonstrates support of spinal cord repair due to its self-renewing and multipotential nature. In addition to physical examinations prior to stem cell procedure and 6 months post-procedure, laboratory test results serve as evidence of repair process. Recognized lab tests for monitoring spinal cord injuries include:
- Review of Medical and Medication History
- Complete physical exam (vital signs of sitting blood pressure, temperature, and heart rate)
- Serum or urine pregnancy test (women of childbearing age)
- Frankel Score   • ASIA Scale   • Manual Muscle Test

2. PRELIMINARIES

A. Background: A spinal cord injury (SCI) is defined as damage to any part of the spinal cord or to the nerves at the end of the spinal canal. Often enough, these damages cause permanent changes in sensation and strength. When an injury occurs to the spinal cord, the outcome is dependent upon where in the spine the damage occurs and how many axons/cells are damaged. Less damage to the cells, leads to greater recovery. Loss of function occurs below the site of injury. Meaning, the higher on the spine the injury occurs, the larger the loss of function will be. Currently, there are an estimated 12,000 SCIs yearly in the United States, while over a quarter of Americans presently live with these injuries. Most of these injuries are caused by car accidents (36.5%), a quarter caused by falls, and the rest are due to violence, sporting accidents, etc. The average age at injury is currently 42.6 and seems to occur mostly in men.

B. Types of the Condition: The severity of the injury can be defined by its “completeness.”
- Complete: Almost all feeling and all ability to control movement are lost below the spinal cord injury. Both sides of the body are equally affected.
- Incomplete: There is control of movement or feeling below the affected area. There are varying degrees of incomplete 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.

Additionally, paralysis from a spinal cord injury may be referred to as:
- Tetraplegia: Also known as quadriplegia, this means your arms, hands, trunk, legs and pelvic organs are all affected by your spinal cord injury.
- Paraplegia: This paralysis affects all or part of the trunk, legs and pelvic organs.

C. Causes: Spinal Cord Injuries are caused by damage to the spinal column or spinal cord. This can stem from fractured, dislocated, crushed, or compression of one or more vertebrae due to trauma. Additionally, a gunshot or knife wound that penetrates to the spinal cord may also be a cause. Supplementary damage may be present if there is bleeding, swelling, inflammation, and fluid accumulation in and around the spinal cord. There are numerous non-traumatic causes, such as: arthritis, cancer, inflammation, infections, or disk degeneration in the spine.
D. Treatment: There is no treatment to reverse the damage of the spinal cord.

- **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. If given within the first eight hours of injury, there can be mild improvement experienced.
- **Immobilization:** Traction can help bring the spine into proper alignment and/or stabilize the spine. A rigid neck collar may help.
- **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. POTENTIAL BENEFITS OF STEM CELL TREATMENT

Studies have shown that the transplantation of mesenchymal stem cells (MSCs) support spinal cord repair due to their self-renewing and multi-potential nature. MSCs can differentiate into distinct cell lineages and have been known to give rise to neural-like cells (neurons and glia) [1]. Transplanted stem cells promote neural regeneration and rescue impaired neural function after SCI by para-secreting permissive neurotrophic molecules at the lesion site to enhance the regenerative capacity thereby providing a scaffold for the regeneration of axons and replacing lost neurons and neural cells [2]. Adipose derived mesenchymal cells inhibit H2O2-mediated apoptosis in spinal cord-derived neural progenitor cells, improving cell survival [2].

### 4. 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 3-5 ml normal saline intrathecally
- **c. Recommended dosing:** Recommended repeat dosing MSC’s every 6 to 8 weeks

### 5. POTENTIAL RISKS OF STEM CELL INJECTION(S)

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 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 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
- Paralysis
- Unknown injuries up to and including death
- Vomiting

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.

### 6. FREQUENTLY ASKED QUESTIONS

1. **What are adults 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, which is what makes them a potential treatment to alleviate and improve degenerative conditions. 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.
1. What is Adipose-derived stem cells and what makes it unique?
Adipose-derived stem cells are stem cells found in the adipose tissue of the patient. The adipose tissue is an abundant source of mesenchymal stem cells which have shown the most healing potential. Adipose Stem cells are autologous (patients stem cells); therefore, having low risk of immune rejection once the therapy has been completed.

2. How can stem cell therapy help treat Spinal Cord Injuries?
MSCs can differentiate into distinct cell lineages and have been known to give rise to neural-like cells (neurons and glia) [1]. Through the use of these MSCs, the goal is regeneration of axons, prevention of apoptosis, replacement of lost cells in order to facilitate remyelination [2].

3. How will the stem cells be delivered to the patient?
The cells will be injected by lumbar puncture (lower portion of back) intrathecally, below where the spinal cord ends. This is similar to the way an epidural would be given.

4. How long do you think it would be before I see some improvement?
The response to the treatment varies from patient to patient. Some patients see a response within the first three months, while many studies have shown patients can improve 6-12 months after a stem cell treatment. This is an ongoing research topic and results are not guaranteed.

5. How long does the procedure take?
The procedure will take approximately 3-4 hours. If you are traveling out of town, you will need to stay in the local area the night of the procedure.

7. SUPPORTING ARTICLES


Stem cell transplantation for spinal cord injury: a meta-analysis of treatment effectiveness and safety.
Fan X1, Wang JZ1, Lin XM1, Zhang L1,2.

Author information
1 Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian Province, China.
2 Xiamen Medical College, Xiamen, Fujian Province, China.

Abstract

OBJECTIVE:
The aim of this study was to evaluate the effectiveness and safety of stem cell transplantation for spinal cord injury (SCI).

DATA SOURCES:
PubMed, EMBASE, Cochrane, China National Knowledge Infrastructure, China Science and Technology Journal, Wanfang, and SinoMed databases were systematically searched by computer to select clinical randomized controlled trials using stem cell transplantation to treat SCI, published between each database initiation and July 2016.

DATA SELECTION:
Randomized controlled trials comparing stem cell transplantation with rehabilitation treatment for patients with SCI. Inclusion criteria: (1) Patients with SCI diagnosed according to the American Spinal Injury Association (ASIA) International standards for neurological classification of SCI; (2) patients with SCI who received only stem cell transplantation therapy or stem cell transplantation combined with rehabilitation therapy; (3) one or more of the following outcomes reported: outcomes concerning neurological function including sensory function and locomotor function, activities of daily living, urination functions, and severity of SCI or adverse effects. Studies comprising patients with complications, without full-text, and preclinical animal models were excluded. Quality of the included studies was evaluated using the Cochrane risk of bias assessment tool and RevMan V5.3 software, provided by the Cochrane Collaboration, was used to perform statistical analysis.

OUTCOME MEASURES:
ASIA motor score, ASIA light touch score, ASIA pinprick score, ASIA impairment scale grading improvement rate, activities of daily living score, residual urine volume, and adverse events.
CONCLUSION: Stem cell transplantation was determined to be an efficient and safe treatment for SCI and simultaneously improved sensory and bladder functions. Although associated minor and temporary adverse effects were observed with transplanted stem cells, spinal cord repair and axon remyelination were apparent. More randomized controlled trials with larger sample sizes and longer follow-up times are needed to further validate the effectiveness of stem cell transplantation in the treatment of SCI.

KEYWORDS: bone marrow mesenchymal stem cells; cell transplantation; human embryonic stem cells; metaanalysis; nerve regeneration; neural regeneration; neural stem cells; paraplegia; spinal cord injury; stem cells; umbilical cord blood stem cells

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Bone Marrow Mesenchymal Stem-Cell Transplantation Promotes Functional Improvement Associated with CNTF-STAT3 Activation after Hemi-Sectioned Spinal Cord Injury in Tree Shrews.

Xiong LL1,2, Liu F1, Lu BT2, Zhao WL1, Dong XJ3, Liu J2, Zhang RP4, Zhang P2, Wang TH1,2.

Author information
1 Institute of Neurological Disease and Department of Anesthesiology, Translational Neuroscience Center, West China Hospital, Sichuan University Chengdu, China.
2 Institute of Neuroscience, Animal Zoology Department, Kunming Medical University Kunming, China.
3 Key Laboratory of National Physical Fitness and Altitude Training Adaptation in Yunnan Province, Institute of Physical Education, Yunnan Normal University Kunming, China.
4 Biomedical Engineering Research Center, Kunming Medical University Kunming, China.

Abstract
Hemi-sectioned spinal cord injury (hSCI) can lead to spastic paralysis on the injured side, as well as flaccid paralysis on the contralateral side, which can negatively affect a patient’s daily life. Stem-cell therapy may offer an effective treatment option for individuals with hSCI. To examine the role of bone marrow mesenchymal stem cells (BMSCs) transplantation on hSCI and explore related mechanisms in the tree shrews, here, we created a model of hSCI by inducing injury at the tenth thoracic vertebra (T10). Hoechst 33342-labeled BMSCs derived from adult tree shrews were isolated, cultured, and implanted into the spinal cord around the injury site at 9 days after injury. The isolated BMSCs were able to survive, proliferate and release a variety of neurotrophic factors (NTFs) both in vitro and in vivo. At 28 days after injury, compared with the sham group, the hSCI group displayed scar formation and dramatic elevations in the mean interleukin 1 beta (IL-1β) density and cell apoptosis level, whereas the expression of signal transducer and activator of transcription 3 (STAT3) and ciliary neurotrophic factor (CNTF) mRNA was reduced. Following BMSC transplantation, motoneurons extent of shrinkage were reduced and the animals’ Basso, Beattie, and Bresnahan (BBB) locomotion scale scores were significantly higher at 21 and 28 days after injury when compared with the injured group. Moreover, the hSCI-induced elevations in scar formation, IL-1β, and cell apoptosis were reduced by BMSC transplantation to levels that were close to those of the sham group. Corresponding elevations in the expression of STAT3 and CNTF mRNA were observed in the hSCI + BMSCs group, and the levels were not significantly different from those observed in the sham group. Together, our results support that grafted BMSCs can significantly improve locomotor function in tree shrews subjected to hSCI and that this improvement is associated with the upregulation of CNTF and STAT3 signaling.

KEYWORDS: CNTF; STAT3; bone marrow mesenchymal stem cells; cell apoptosis; cell transplantation; spinal cord injury; tree shrews

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NING ZHANG1, JOHANNES WIMMER2, SHENG-JUN QIAN1 AND WEI-SHAN CHEN1“
1Department of Orthopaedics, 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People’s Republic of China for Orthopedics, Campus Luebeck, University Medical Center Schleswig-Holstein, Luebeck, Germany

ABSTRACT
Spinal cord injury (SCI) invariably results in the loss of neurons and axonal degeneration at the lesion site, leading to permanent paralysis and loss of sensation. There has been no successful treatment for severe spinal cord injuries to recover back to normal function yet. Studies have shown that the transplantation of stem cells may provide an effective treatment for SCI because of the self-renewing and multipotential nature of these cells. Stem cells have the capability to repair injured nervous tissue through
replacement of damaged cells, neuroprotection, or the crea-
tion of an environment conducive to regeneration by endogenous
cells. Up to today several types of stem cells have been transplanted into the injured spinal cord. However, the question of which
cell type is most ben-

eficial for SCI treatment is still unresolved. There are still several limita-

Venkata Ramesh Dasari, Krishna Kumar Veeravalli, Dzung H Dinh

Abstract

With technological advances in basic research, the intricate mechanism of secondary delayed spinal cord injury (SCI) continues
to unravel at a rapid pace. However, despite our deeper understanding of the molecular changes occurring after initial insult to
the spinal cord, the cure for paralysis remains elusive. Current treatment of SCI is limited to early adminis-
tration of high dose steroids to mitigate the harmful effect of cord edema that occurs after SCI and to reduce the cascade of secondary delayed SCI.
Re-
cent evident-based clinical studies have cast doubt on the clinical benefit of steroids in SCI and intense focus on stem
cell-based therapy has yielded some encouraging results. An array of mesenchymal stem cells (MSCs) from various sources
with novel and promising strategies are being developed to improve function after SCI. In this review, we briefly discuss
the pathophysiology of spinal cord injuries and characteristics and the potential sources of MSCs that can be used in the treatment
of SCI. We will discuss the progress of MSCs application in research, focusing on the neuroprotective properties of MSCs.
Finally, we will discuss the results from preclinical and clinical tri-
als involving stem cell-based therapy in SCI.

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