Stem cell therapy for traumatic spinal cord injury

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Disclosures
None
Objectives

• **Learn**: types of stem cell therapy (SCT) for SCI

• **Understand**: state of research about effectiveness of SCT for SCI

• **Apply and Evaluate**: safety, risks, and potential benefits of participating in a stem cell therapy, clinic, or study
Outline

1. Background and types of stem cells
2. Review of current study results
3. Ethics of stem cell therapy and questions for future studies
ONE SMALL STEP
A paralysed underdog pioneering surgery.
BY D.T. MAX

When a spinal cord is damaged, location is destiny: the higher the injury, the more severe the effect. The spine has thirty-three vertebrae, which are divided into five regions—the coccyx, the sacral, the lumbar, the thoracic, and the cervical. The nerve-rich cord traverses nearly the entire length of the spine. The nerves at the bottom of the cord are well burried, and sometimes you can walk away from damage to these areas. In between are insults to the long middle region of the spine, which begins at the shoulders and ends at the midriff. These are the thoracic injuries. Although they don't affect the upper body, they still take away the ability to walk or feel below the waist, including autonomic function (bowel, bladder, and sexual control). Injuries to the cord in the cervical area—what is called "breaking your neck"—can be lethal or leave you paralyzed and unable to breathe without a ventilator.

Doctors who treat spinal-cord-injury patients use a letter-and-number combination to identify the site of the damage. They talk of C8 (the cord as it passes through the third cervical vertebrae) or T4 (the eighth thoracic vertebrae). These morbid bingos-like codes help doctors instantly gauge the severity of a patient's injury.

Darek Fidyka, who is forty-one years old, is a T9. He was born and raised in Pradzow, a small farming town in central Poland, not far from Lodz. At 3 A.M. on July 26, 2010, Fidyka and his girlfriend, Justyna, woke up to the sound of someone smashing Fidyka's Volkswagen outside their house, a few miles from Pradzow. They got out of bed, rushed out the door, and found her ex-husband, Jaroslaw, bashing the car with a cinder block. They were not completely shocked. The three of them had been friends since their ten years—Fidyka had gone to Justyna and Jaroslaw's wedding—but Jaroslaw eventually became a heavy drinker. He started beating Justyna, and then went to prison for it. Justyna obtained an order of protection, and eventually took up with Darek. He moved into her house. "Our earlier relationships hadn't worked out, so we decided to give it a try," Fidyka recalls. But Jaroslaw, consigned, believed that his two friends had begun a relationship while he and Justyna were still married.

Outside the house, Fidyka and Justyna tried to calm Jaroslaw down. Though Fidyka was tall and athletic—he was a contractor and a volunteer fireman—Jaroslaw pounced on him. "I didn't expect him to have a knife," Fidyka says. Jaroslaw stabbed him eighteen times. Several of the wounds punctured his lungs, and one nearly cut his spinal cord in half.

As Fidyka lay on the ground, he felt his body change. "I can remember very vividly losing feeling in my legs, bit by bit," he says. "It started in the upper part of the spine and was moving down slowly while I lay waiting for the ambulance to arrive." He adds, "I was aware of everything. I could feel my strength leaking out with every thrust." Jaroslaw dropped his weapon and ran away. He hanged himself shortly afterward, in a nearby orchard.

Today, Fidyka lives at Alkon, a rehabilitation facility in Winnica, a city in western Poland. The attack left him paralyzed from the waist down. The Alkon facility is affiliated with the city's university hospital—Winnica is the former German city of Breslau, long a place of medical excellence—and occupies a two-story building on the outskirts. The long, low structure, a former Hare Krishna center, was built on open land, but it is being walled in as Poland proceeds and new buildings are constructed. Fidyka lives in a narrow room on the second floor. He has a laptop and a few books; the only picture on the wall is of Pope John Paul II. Justyna left him six months after the knifing.

On the day I met a bowl of dandelions—Fidyka, who lives in Pradzow. Many nights he died in the bed. Her scuffs are in sneakers, which Fidyka keeps downstairs in an effort to gain back his balance on them one spring, as a physiologist's stance. One problem for the staff is what should provide artificial that are meant to lay near two times, who had been part of a car whose spine had an operation for lying face down on a bed was sitting up, pulling up on therapy is not one. It is intimate and the just as the well and the decor at every. Fidyka looked up and took his energy. When you do pay hours a day, five days a week. Fidyka is a student. People with a can get better, but within the first few months, it is not unusual for a patient, especially one with partial spinal-cord damage, to regain some strength or sensation in the legs, or some bowel control or sexual function. But after this period the likelihood of improvement drops off radically. Scar
Why stem cells?

- Ability to become any type of cell (almost)
- Readily available from multiple sources
- If autologous (from self), low risk of rejection
Stem cells: a primer
Where do stem cells come from?

• Autologous – from self
• Allogenic – from other people
Totipotent zygote stem cell  \[\rightarrow\]  pluripotent embryonic stem cell

**ENDODERM**
- Intestine, lungs, glands

**MESODERM**
- Mesenchymal SC (stromal cells)
  - Bone, cartilage, muscle, marrow, adipose
- Hematopoietic SC
  - Blood

**ECTODERM**
- Skin, nervous system

Fertilized egg
Totipotent
Zygote
Can become anything

Multipotent
Adult stem cells
Can become some things

Pluripotent
Induced pluripotent (iPSCs)
Can become most things

Embryonic
Potency as it relates to stem cells
Types of cells used in reviewed studies
Neural stem/progenitor cells (precursor brain cells)

MSCs

Hematopoietic

Schwann (nerve)
Outline

1. SCI epidemiology and types of stem cells
2. **Review of current study results**
3. Ethics of stem cell therapy and questions for future studies
Search through medical literature

Filter: Humans, English

329 articles identified through primary search

294 articles excluded for nonhuman studies, not in English, errors in classification

4 articles identified from references of primary search

39 articles in final analysis

978 patients total

Not every search result is a good one

Read and analyzed
Variables

- Timing after injury
- Completeness
- Type of cells
- Dose of cells
- Route of administration
Who were in these studies?

- Mix of patients with chronic and acute injuries, paraplegia and tetraplegia, complete and incomplete
- Majority of patients had chronic injuries, mix of paraplegia or tetraplegia, and were complete
Cell Types

The majority of studies in this review assessed the effects of **autologous MSCs** as treatment for SCI.
Totipotent zygote stem cell ➔
pluripotent embryonic stem cell

ENDODERM
- Intestine, lungs, glands

MESODERM
- Hematopoietic SC
- Bone, cartilage, muscle, marrow, adipose

ECTODERM
- Skin, nervous system

Mesenchymal SC (stromal cells)
- Blood

Stem cell therapy: did it help?

Change in AIS (ASIA) classification (A-E)

39 studies

26 documented AIS

18 Benefit
8 No benefit
It helped! What’s the problem?

• These studies were all very different
  • different injury levels, completeness, time since injury, cells used, number in study, non-randomized, non-blind
• Although these were in “peer-reviewed” journals, overall they are not very “strong” studies
“[Of those with neurologically complete injuries at 1 year], 3.5% improved to AIS B, and up to 1.05% each improved to AIS grades C and D at 5 years post injury”
## Patterns of Sacral Sparing Components on Neurologic Recovery in Newly Injured Persons With Traumatic Spinal Cord Injury

<table>
<thead>
<tr>
<th>Initial AIS grade</th>
<th>AIS Grade at Discharge (%)</th>
<th>AIS Grade at 1 Year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>A</td>
<td>80.2</td>
<td>13.1</td>
</tr>
<tr>
<td>B</td>
<td>5.0</td>
<td>53.4</td>
</tr>
<tr>
<td>C</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>D</td>
<td>0.4</td>
<td>0</td>
</tr>
</tbody>
</table>
Study example of "success"

Korean study that used autologous MSCs into the spinal cord or spinal space (via spinal tap):

• Patient 1 (8 months from injury) started at less than antigravity strength in elbow flexors/extensors and wrist extensors and returned to near-full strength in those muscles at 40 months post-treatment

• Patient 2 (38 months from injury) started at antigravity strength in elbow extensors and regained full strength in those muscles at 39 months post-treatment

• Patient 3 (96 months post injury) started at flicker to near-anti-gravity strength in finger muscles and regained full strength in those muscles at 30 months post-treatment
## Expected functional outcomes

### TABLE 6. Expected Functional Outcomes

<table>
<thead>
<tr>
<th><strong>Low endurance and vital capacity secondary to paralysis of intercostals; may require assist to clear secretions</strong></th>
<th><strong>Level C5</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Low endurance and vital capacity secondary to paralysis of intercostals; may require assist to clear secretions</td>
<td><strong>Level C5</strong></td>
</tr>
<tr>
<td>Bowel</td>
<td>Total assist</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Bladder</td>
<td>Total assist</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Bed Mobility</td>
<td>Some assist</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Bed/Wheelchair Transfers</td>
<td>Total assist</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Pressure Relief/Positioning</td>
<td>Independent with equipment</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Eating</td>
<td>Total assist for setup, then independent eating with equipment</td>
<td>2-5.5</td>
</tr>
<tr>
<td>Dressing</td>
<td>Lower extremity: Total assist</td>
<td>1-4</td>
</tr>
<tr>
<td>Grooming</td>
<td>Some to total assist</td>
<td>1-6</td>
</tr>
<tr>
<td>Bathing</td>
<td>Total assist</td>
<td>1-3</td>
</tr>
<tr>
<td>Wheelchair Propulsion</td>
<td>Power: Independent Manual: Independent to some assist indoors on nonslippery surfaces, some to total assist outdoors</td>
<td>5-6</td>
</tr>
<tr>
<td>Assist Required</td>
<td>Personal care: 10 hours/day</td>
<td>16-23</td>
</tr>
<tr>
<td><em>Hours per day.</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 6. Expected Functional Outcomes

<table>
<thead>
<tr>
<th><strong>Level C6</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Bowel</td>
</tr>
<tr>
<td>Bladder</td>
</tr>
<tr>
<td>Bed Mobility</td>
</tr>
<tr>
<td>Bed/Wheelchair Transfers</td>
</tr>
<tr>
<td>Pressure Relief/Positioning</td>
</tr>
<tr>
<td>Eating</td>
</tr>
<tr>
<td>Dressing</td>
</tr>
<tr>
<td>Grooming</td>
</tr>
<tr>
<td>Bathing</td>
</tr>
<tr>
<td>Wheelchair Propulsion</td>
</tr>
<tr>
<td>Assist Required</td>
</tr>
<tr>
<td><em>Hours per day.</em></td>
</tr>
<tr>
<td>FIM Score</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

**Spinal Cord Injury CPG 1999**

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### TABLE 6. Expected Functional Outcomes

<table>
<thead>
<tr>
<th>Equipment</th>
<th>FIM/Assistance Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating: Total assist for setup, then independent eating with equipment</td>
<td>5 5 25-55</td>
</tr>
<tr>
<td>Eating: Independent with or without equipment; except cutting, which is total assist</td>
<td>1 1 1-4</td>
</tr>
<tr>
<td>Dressing: Upper extremity; total assist</td>
<td>1-3 1 1-5</td>
</tr>
<tr>
<td>Dressing: Independent upper extremity; some assist to total assist for lower extremities</td>
<td>1 3-6 1-5</td>
</tr>
<tr>
<td>Grooming: Upper body: Independent</td>
<td>1-3 1 1-3</td>
</tr>
<tr>
<td>Grooming: Some to total assist</td>
<td>1 1 1-1</td>
</tr>
<tr>
<td>Bathing: Upper body: Independent</td>
<td>1 1 1-1</td>
</tr>
<tr>
<td>Bathing: Lower body: Some to total assist</td>
<td>1 1 1-1</td>
</tr>
<tr>
<td>Wheelchair Propulsion: Independent</td>
<td>6 6 5-6</td>
</tr>
<tr>
<td>Wheelchair Propulsion: Power: independent with standard arm drive on all surfaces Manual: Lightweight rigid or folding frame with handrim modifications</td>
<td>6 6 5-6</td>
</tr>
<tr>
<td>Assist Required</td>
<td><em>Personal care: 10 hours/day</em></td>
</tr>
<tr>
<td><em>Hours per day.</em></td>
<td></td>
</tr>
</tbody>
</table>

**Level C5**

**Level C6**

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Adapted devices as indicated (e.g., u-cuff, tendinous splint, adapted utensils, plate guard)
INTERNATIONAL PATIENTS

Spinal Cord Reconstruction and Stem Cell Implantation: Spinal Cord Injury in Beijing China

At Beijing Puhua International Hospital, the price for the Spinal Cord Reconstruction and Stem Cell Implantation package starts from $30,780 (4 weeks, nonsurgical) and $33,813 (3 weeks, cervical segment).

Package price: $30,780

Best Stem Cell Therapy for Spinal Cord Injury in Europe

Are you tired of bad treatments? Would you like to enjoy life like you did before? Don’t worry we got the right thing for you. You can enjoy walks with your family again for just $7,000.

Package price: $7,000

Stem Cell Therapy in India for Severe Spinal Cord Injury

Choose our elite stem cell therapy for severe spinal cord injury and get back on your feet right now! ReStem is one of the most reputed centers in India for Stem Cell Therapy treatments especially for severe injuries such as spinal cord and neurological affections.

Package price: $9,900

Stem Cell Therapy for ALS in Vienna Austria

The stem cell therapy for ALS can help patients struggling with the condition to improve their health, by relieving the symptoms and slowing the progression of the disease.
Beike is only using adult stem cells (also called somatic stem cells) in its treatment protocols and does not provide embryonic stem cells. It is important to remember that while embryonic stem cells may have more regenerative potential, there may also be serious medical complications. At Beike Biotechnology, our treatment protocols do not compromise or trigger concerns about adults stem cells.

The adult stem cells provided in our treatment protocols come from two distinct sources: umbilical cord tissue and umbilical cord blood. This allows us to provide our patients with Umbilical Cord Blood Stem Cells (UCBSC) and Umbilical Cord Mesenchymal Stem Cells (UCMSC) separately or in combination depending on each patient's specific condition and need. Umbilical cord-derived stem cells do not draw any concern from the scientific community and have been proven effective for a wide range of conditions.

22,500 patients with no serious adverse reaction reported.
An adverse event or suspected adverse reaction is considered “serious” if [...] it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
Risks

• 18 year old woman at time of injury
• 3 years later underwent olfactory (nasal cell) transplant
• 8 years later had back pain

What is this?
Why aren’t there more stem cell trials for SCI?

• Lack of standardization (type of stem cell, dose, route)
• Difficult to randomize and/or control, small study sizes
• FDA approval (usually lacking or slow)
• Expensive (cost of treatment, travel, sick time)
• Unclear level of risk
Outline

1. SCI epidemiology and types of stem cells
2. Review of current study results
3. Ethics of stem cell therapy and questions for future studies
What’s ethics got to do with it?
The first consent should be obtained before operation shortly after the injury occurs, but in this case the patient was sedated and his family was upset,
Medical Vulnerability

“Social groups who have an increased relative risk or susceptibility to adverse health outcomes”
Balance in reporting: is it #fakenews?

On SCI Advocacy websites that mentioned stem cells...

Positive:negative statements **10:1**

Ethics-related information comprised **20%** of total content

Parke 2010
Risks of social media

Most SCI tweets pertaining to stem cell therapy

neutral or positive
“What would you want your chances to be for getting some functional recovery back?”

Minimum chance of functional recovery required for entering a SCT research trial
Risk-taking

Kwon 2012
The literature supports that:

- Majority of stem cell therapy information is neutral or positive, both on websites and social media.
- Majority of respondents (8 of 10) would be satisfied with 1-50% chance of functional recovery from SCT.
- Up to 25% of respondents willing to participate in SCT regardless of risk.
Questions when reviewing future studies

Were assessments performed in a blinded manner?

Were participants followed and observed for at least 4 months after the treatment?

Are the results reproducible?
Essential questions to ask a stem cell clinic

- Is the treatment FDA-approved, and if not, why not?
- Will this affect whether I can get into another clinical trial?
- What benefits can I expect?
- How will this be measured, and how long will it take?
Essential questions to ask a stem cell clinic

- What other medications or special care might I need?
- How is this stem cell procedure done?
- What is the source of the stem cells?
- How are the stem cells identified, isolated, and grown?
Essential questions to ask a stem cell clinic

- Are the cells differentiated into specialized cells before therapy?
- How do I know if the cells are delivered to the right part of my body?
- If the cells are not my own, how will my immune system be prevented from reacting to the transplanted cells?
- What do the cells actually do, and is there scientific evidence that this procedure could work for my disease or condition? Where is this published?
On the horizon...

Hospital Sao Rafael – autologous MSCs
Ferrer – allogenic MSCs
Sun Yat Sen – umbilical MSCs
Beijing – MSCs or NSCs on collagen scaffold
Miami – autologous Schwann
Da Nang – autologous mononuclear
Sci star – oligodendrocyte progenitor
UCSD – neural stem
BioArctic – FGF1 and peripheral nerve
Non-SCT

<table>
<thead>
<tr>
<th>SPRING trial</th>
<th>VX-201/Cethrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eusol</td>
<td>rFGF</td>
</tr>
<tr>
<td>Rick Hansen</td>
<td>Minocycline</td>
</tr>
<tr>
<td>RISCIS</td>
<td>Riluzole</td>
</tr>
<tr>
<td>Kringle</td>
<td>Hepatocyte GF</td>
</tr>
<tr>
<td>OSU</td>
<td>Glyburide</td>
</tr>
<tr>
<td>Kessler</td>
<td>Dalfampyridine</td>
</tr>
<tr>
<td>Others</td>
<td>Hypothermia, HBO, AIH, BP</td>
</tr>
</tbody>
</table>
I’m interested in learning more... what do I do next?
How do I learn more about clinical trials?

Find NIH Clinical Center Trials

The National Institutes of Health (NIH) Clinical Center Search the Studies site is a registry of publicly supported clinical studies conducted mostly in Bethesda, MD.

Keyword: [Enter Diagnosis or Keyword]

Search
Take-home points

• Stem cell therapy for spinal cord injury has shown some benefit, but is not without risks of its own; additionally, “benefits” are not guaranteed
• If you are considering stem cell therapy: Do your homework!
• Beware of anecdotal evidence or testimonials
• If it sounds too good to be true, it probably is
Acknowledgements
References continued


References continued


