Stem Cell Therapy in Chronic Spinal Cord Injuries

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ABSTRACT

Background: Stem cell therapy has shown to have considerable therapeutic potential for spinal cord injuries (SCIs). The use of bone marrow stromal cells (BMSCs) is clinically attractive because they have shown therapeutic potential in SCI and can be obtained in patients at bedside, raising the possibility of autologous transplantation. Objectives: To study the value (BMSCs) injected intra-thecally to enhance the repair process in patients with chronic SCIs. Methods: Sixty three patients with Chronic SCI, 43 patients were given stem cell therapy intra-thecally monthly for six months. Twenty patients were clinically followed up as a control group, all underwent neurological examination; (Motor and Sensory Indices, Ashwarth Spasticity Scale, Functional Ambulation Categories (FAC) and Classify our patients according to American Spinal Injury Association (A, B, C, D or E). Somatosensory evoked potential [SEP] (pre and post (6 months) injections). Results: We found improvement in the motor power [p = 0.001], bladder [p>0.001] and bowel control [p=0.003], there was a significant change from ASIA A to ASIA B [p=0.001], improvement in the cortical potential of SEP [p=0.04], increase in the tone (spasticity) [p>0.001], improvement in the FAC score in 11/ 43 and increased incidence of neuropathic pain in 24 out of the 43 patients (55.8% - p>0.001) in the treated group. In the control group, there was improvement in the bladder control [p = 0.05], increase in the tone [p=0.06], but no significant change in the motor power, bowel control, or the incidence of neuropathic pain. Conclusion: Stem cell therapy is a safe treatment option for patients with chronic SCI, further follow-up and research will be needed to adequately define the role of this new treatment modality in patients with chronic SCI. (Egypt J. Neurol. Psychiat. Neurosurg. 2009, 46(2): 467-478)

Keywords: Autologus stem cell, spinal cord injury, SSEP

INTRODUCTION

Therapeutic cell transplantation has shown great promise in the treatment of many neurological disorders including spinal cord injury (SCI). Several cell types have been investigated and many potential candidates have been identified including embryonic stem cells, olfactory ensheathing glial cells and Schwann cells. The bone marrow also contains at least two, and likely more, discernable stem cell populations. Besides the hematopoietic stem cells, which are used regularly to treat haematological diseases, another cell type termed mesenchymal stem cell (MSC) also exists in the bone marrow. MSCs have the ability to transdifferentiate themselves when in a different environment to take on the cell functions of the new tissue. They are also described as having homing properties which is their ability to detect and migrate towards injured tissues

Bone marrow MSCs are particularly attractive clinically because of their availability. Bone marrow samples can be obtained from the patients at the bed-side. This is followed by isolation of MSC which is based on detection of certain cell surface markers and on the ability of these cells to form adherent cell layers in culture. These cells are then expanded in culture and transplanted back into the patient. Thus an autologous model of cell therapy in humans is carried out. By using the autologous model, we can eliminate or minimize the problems associated with embryonic stem cells that include the ethical and technical considerations of obtaining

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embryonic tissues, the need for long-term immunosuppression of the recipients, and the possibility of transmitting infectious agents with the transplanted cells.

Theoretically and clinically, intrathecal delivery of stem cells through lumbar puncture (LP) is extremely attractive. LP is a minimally invasive procedure that can be performed at the bedside. Bone marrow derived MSCs in vivo appear to be able to form neuronal tissues. Kabos et al. treated unfractionated bone marrow in culture with epidermal growth factor and basic fibroblast growth factor. This gave rise to neurospheres expressing neural markers after the stem cells were injected into the area of damage in the spinal cord. Remyelination of the area was later seen. The authors noted that the effect was more pronounced when the stromal cells were injected one week after injury rather than immediately after. Another study injected MSCs into rats subjected to weight driven implant injury. Their data indicated significant improvement in functional outcome in animals treated with MSC transplantation compared to control animals injected with saline. Scattered cells derived from MSCs expressed neural protein markers. These data suggest that transplantation of MSCs may have a therapeutic role after spinal cord injury. However it appears that restoring spinal cord function requires reconstruction of complex neuronal circuitry, and it is likely that a "cocktail" of treatments or cell types will be required, possibly cells of both glial and neuronal origin.

Bone marrow MSCs were also shown to improve demyelinating types of injury through producing growth factors which activate the protein kinase B (Akt) pathway and increase the survival of oligodendrocytes (OLG). MSCs also reduce p75 and caspase 3 expressions in the oxygen-glucose deprivation -OLGs, which leads to decreased OLG apoptosis. MSCs participate in OLG protection that may occur with promoting growth factors/PI3K/Akt and inhibiting the p75/caspase pathways. Transplantation of these cells by direct microinjection into the demyelinated spinal cord of the immunosuppressed rat resulted in remyelination. The remyelinated axons showed characteristics of both central and peripheral myelination as observed by electron microscopy and improvement of conduction velocity of the axons. These findings indicate that MSCs can form functional myelin during transplantation into demyelinated spinal cord.

**Aim of Work:**

To study the safety and efficacy of bone marrow MSCs injected intrathecally in patients with chronic spinal cord injuries.

**MATERIAL AND METHODS**

Sixty four patients with traumatic or post-inflammatory chronic spinal cord injuries were enrolled into the study. Their age ranged from 18 to 60 years, and both genders were included in the study. Forty four patients were given stem cell therapy intrathecally, while 20 patients were clinically followed up as a control group. The patients were recruited from the outpatient clinic of physical medicine in Cairo University Hospitals. All patients were receiving the same rehabilitation program throughout the time of the study. One patient dropped out during the course of the study. Thus, statistical analysis was performed on 43 treated patients and 20 control patients. At the time of enrollment, all subjects suffered from spinal cord injury that showed a stationary course for the previous six months. Their injury was a single spinal cord lesion between the third cervical and the twelfth thoracic levels. Surgery had no role in the management of these patients.

Ethical approval for this study was obtained from the ethical committee of National Cancer Institute Cairo University. Informed consent obtained and consent form signed from all participants.

Patients were excluded if they had a source of infection in the lumbar region, a coagulation defect, an injury of less than one year duration or were pregnant.

The patients underwent the following:

- Thorough clinical history and neurological examination.
- Trunk muscle assessment according to the following levels:
  - **Level I:** Establishing the upright posture
  - **Level II:** Basic trunk movement components
  - **Level III:** Coordinated trunk and extremity patterns
  - **Level IV:** Power production
- Completion of Visual analogue scale (for pain assessment)\(^\text{14}\).
- Measurement of spasticity using Modified Ashworth Spasticity Scale\(^\text{15}\).
- Classification according to Functional Ambulation categories\(^\text{16}\).
- Classification according to ASIA protocol which evaluates motor and sensory functions on both sides of the body and uses an impairment scale of A to E as follows: A (no motor or sensory function in the sacral segments S4-S5), B (sensory improvement with out motor improvement below the neurological level), C (Some sensory and motor improvement), D (useful motor function), E (normal function)\(^\text{17}\).
- Bladder and Bowel control assessment\(^\text{18}\).

The rehabilitation program for all participants included mat activities, transferring activities, independent self-range of motion\(^\text{19}\), strengthening exercises, ambulation training for paraplegic patients\(^\text{20}\), upright posture on the tilting table\(^\text{21}\) and cardiopulmonary training\(^\text{21},\text{22}\).

**Neuropathological Assessment:**
Lower limb somatosensory evoked potentials (SSEP) were recorded by stimulating the posterior tibial nerve and recording from the somatosensory cortex. The posterior tibial nerve was stimulated transcutaneously using electrodes placed on the skin over the nerve. Recording was carried out using standard EEG disk electrodes. They were placed over the somatosensory cortex for recording cortical potentials, and over the lumbar spine for recording the lumbar potential. Somatosensory evoked potentials were recorded before and after 12 months of injections.

Magnetic Resonance Image (MRI) was used to determine the site and nature of the lesions and if the cord transection was complete or incomplete. It was also used to exclude patients with cord compression.

**Laboratory Method**

A. **Sampling:**
The posterior iliac spine was sterilized and local anesthesia was applied to the periosteum and skin of that area using 1% xilocaine. Ten to twenty millimetres of bone marrow were aspirated under aseptic conditions on preservative-free heparin.

B. **Sample preparation:**
Mononuclear cells were prepared using density gradient centrifugation on Ficol-Hypaque (density 1017). The cells were suspended in two millimetres of the patient’s own serum with the addition of antibiotics (penicillin/streptomycin) and antifungal (fungisone).

C. **Cell Delivery:**
The stem cells were injected intrathecally in the lumbar region at the L3-4 or L4-5 levels. The dose was 5-10 x 10^6 / Kg of mononuclear cells. The subjects were injected every month for a six months period.

**Statistical Analysis**
Statistical package for social science (SPSS) version 13 was used for data management and analysis. Descriptive analyses were conducted to examine the frequencies and distribution of all variables. To test the significance of difference between qualitative variable among cases and controls, the Chi square test, Fisher exact and Wilcoxon Signed ranks were performed. T test was used to compare means of quantitative variables as age and motor changes among examined groups. Paired t test was used to compare changes in quantitative variables in each group. McNemar test was used to compare changes in diachotomus variables among each group.

**RESULTS**

Our study was a prospective non randomized, case- control study.
Patients Characteristics:

As regards the general characteristics of both the treated and the control groups we found that both groups were matched in all parameters, including neurological and MRI findings (Tables 1 and 2).

Effect of Stem Cell therapy:

Comparisons:

A. Motor Function:

There was minimal improvement in the motor power of the treated group with a mean motor score before and after injections of 49.2±8.9 & 49.8±9.1 respectively, with improvement seen in 17 patients. \[p< 0.001\]. The highly significant value is believed to be contributed to by the small standard deviation inspite of absence of a remarkable improvement clinically. In the control group, the mean motor score before and after follow up was 49±9.8 & 49.2±9.9 respectively, with improvement seen in 2 subjects only \[p=0.18\] (Fig. 1). The degree of improvement in the motor score was significantly better in the treated group than the control group \(p=0.02\).

We did not find a significant difference in the motor score between the quadriplegic (33.3±12.4 & 34.1±12.8) or the paraplegic patients (51.7±4.9 & 52.3±5.1) before and after treatment respectively. The mean percentage of change in the motor score was 2.5±2.7 for the quadriplegic and 1.11±1.5 for paraplegic patients \(p=0.09\)

As regards the trunkal support there was improvement in both the treated and the control groups \(p=0.005\) and \(p=0.01\), respectively. In the treated group, 7 patients improved from level I to level II and one patient showed improvement from level II to level III, whereas in the control group 4 patients improved from level I to level II trunkal support. However, there was no significant difference between the treated patients and the control group. Trunkal support was significantly related to the motor score improvement \(p>0.001\).

There was improvement in the Functional Ambulatory Categories, in both groups, with the treated group showing improvement in 11 subjects (25.6%) and the control group showing improvement in 4 subjects (20%). The change in both groups was from non-functional (i.e. can’t walk) to dependent requiring firm continuous support from one person (level 2). However, there was no difference in the degree of improvement between the treated and the control groups \(p=0.7\). There was also no significant relation between the motor improvement and the Functional Ambulation Category \(p=0.61\).

B. Tone:

We found a significant increase in tone (spasticity) in the treated group \(p<0.001\) while there was no significant change in tone in the control group \(p=0.06\). Grade 3 spasticity was reached in 4 patients in the treated group (9.3%), compared to 1 subject in the control group (5%). We note that in the control group, one patient already had grade 3 spasticity (Fig. 2). The difference in the degree of tone increase between the treated and control groups was not significant \(p=0.3\).

C. Sensory:

a. Sensory Assessment:

Pin prick score (PPs) in the treated group before and after treatment was 53.95±16.7 & 54.18±16.5 respectively \(p=0.058\). On the other hand light touch score (LTs) before and after treatment was 55.53±15.68 & 55.86±15.59 respectively \(p=1\). In the control group PPs before and after treatment was 49.90±23 & 49.95±22.9 respectively \(p=0.33\), while LTs before and after treatment was 51±23 & 51±23.03 \(p=0.044\). When we compared the degree of improvement between the treated and control groups, we did not find a significant difference in either the PPs \(p=0.48\) or the LTs \(p=0.17\).

The level of the lesion did not affect the improvement in the PPs \(p=0.55\) or the LTs \(p=0.68\) as we found no difference between the paraplegic or quadriplegic patients.

b. Pain:

Both the treated and the control subjects did not complain from neuropathic pain prior to the study. During the course of treatment, 24 out of the 43 treated patients (55.8%) developed neuropathic pain \(p<0.001\). None of the control group developed any sort of pain.
D. Bladder
Bladder control was assessed using a questionnaire. Overall there was a significant improvement in the bladder control in the treated and the control population (p>0.001 and p=0.05, respectively). Most of the improvement occurred from the total incontinence to reflex voiding without or with partial sensation. No one in the treated or the control groups reached complete recovery of bladder control. There wasn’t a significant difference between both groups in the degree of bladder control improvement (p=0.1).

E. Bowel
We found a significant improvement in the bowel control in the treated group (p=0.003). In the control population, however, there was not any significant improvement (p=0.16). Most of the improvement occurred from total incontinence to partial control with or without partial sensation. Complete recovery of bowel control was not reached by any subject. There wasn’t a significant difference between both groups in the degree of bowel control improvement (p=0.3).

F. ASIA Scale
In the treated group there was a significant change from ASIA grade A to grade B or grade C. One patient changed from grade A to grade C and eleven patients changed from grade A to grade B (p=0.001). In the control group there were no significant changes in the ASIA scale as only two patients changed from grade A to grade B (p=0.16). The difference between both group regarding ASIA grade improvement showed a tendency towards significance (p=0.07) (Fig. 3).

We found significant correlations in the treated group between the improvement of bowel control (r=0.4, p=0.007) and bladder control (r=0.4, p=0.008) and the change in ASIA scale. However, in the control group, there was not any significant correlation with the ASIA scale changes.

Possible side effects:
The following side effects were recorded in some patients who completed the treatment regimen for stem cell (Table 3):

- One case (2.1%) developed acute disseminated encephalomyelitis, and dropped out of the study.
- Three patients (6.9%) developed excessive sweating below the level of the lesion after the fourth injection and this continued throughout the follow up period.
- Four patients (9.3%) developed marked increase in spasticity that interfered with physical exercise and required botulinum toxin A injection.
- One patient (2.3%) developed marked increase in the tone of the abdominal muscles that resulted in dyspnea which improved on oxygen inhalation and muscle relaxant. This occurred in the immediate post-infusion period and was relieved two hours later.
- One patient (2.3%) developed jerky movements below the level of injury immediately after the first and second injections without any loss of consciousness. This was relieved 1 hour later by benzodiazepine injection.
- Twenty four (55.8%) patients developed neuropathic pain affecting the trunk and lower limbs. Most of them were relieved by gabapentin or oxycarbamazepine.
- Three patients developed transient hypertension for two days after the MSCs injection.

Neurophysiological Assessment:
Somatosensory evoked potentials was performed for 30 patients before and after receiving stem cell therapy. There was an improvement in the SSEP in only three treated patients who showed a cortical potential after initial absence (p= 0.08). No one in the control group (5 patients) showed an improvement in the SSEP.

MRI finding
Type and site of lesion:
Statistical analysis showed that all patients who had myelitis did not show improvement in any of their parameters, unlike the patients who had a traumatic aetiology. Moreover, one of the myelitic patients developed acute disseminated encephalomyelitis, which occurred after the 3rd injection and the patient did not complete the study.
We found a significant positive correlation between the motor improvement in the treated patients and the cord injury being incomplete (p=0.04). We also noted a trend towards significant motor improvement in patients with dorsal lesions more than those with cervical lesions (p=0.08).

Otherwise, we did not find a significant correlation between the MRI determined site or degree of lesion and changes in sensation, bladder or bowel control, ASIA scale, tone, or FAC in both the treated and the control groups.

Table 1. Demographic data and MRI findings of both groups.

<table>
<thead>
<tr>
<th></th>
<th>Treated group (n= 43)</th>
<th>Control group (n= 20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.7±10.4</td>
<td>33.8±11.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Gender</td>
<td>36 males (83.7%)</td>
<td>15 males (75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 females (16.3 %)</td>
<td>5 females (25 %)</td>
<td></td>
</tr>
<tr>
<td>Duration (years) of SCI</td>
<td>3.6±2.5</td>
<td>3.7±2.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Result of MRI of spinal cord according to integrity of cord</td>
<td>Complete cut 12 pts (27.9%)</td>
<td>3 pts (15%)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Incomplete cut 31 pts (72.1%)</td>
<td>17 (85%)</td>
<td></td>
</tr>
<tr>
<td>Result of MRI of spinal cord according to aetiology of injury</td>
<td>Traumatic 40 pts (93%)</td>
<td>19 pts (95%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myelitis 3 pts (7%)</td>
<td>1 pt (5%)</td>
<td></td>
</tr>
<tr>
<td>Result of MRI of spinal cord according to site of injury</td>
<td>Cervical lesion 6 pts (13%)</td>
<td>2 pts (10%)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Dorsal lesion 37 pts (86%)</td>
<td>18 pts (90%)</td>
<td></td>
</tr>
</tbody>
</table>

SCI = spinal cord injuries

Table 2. Result of different scales in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Treated group (n= 43)</th>
<th>Control group (n= 20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASIA Score</td>
<td>Motor score 49.2±8.9</td>
<td>49±9.8</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Pin Prick score 53.95±16.7</td>
<td>49.90±23</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Light Touch score 55.53±15.68</td>
<td>51.00±23</td>
<td></td>
</tr>
<tr>
<td>Trunkal support</td>
<td>Level I 3</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Level II 36</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level III 4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tone (Modified Ashworth Scale)</td>
<td>0 pts (67.44%)</td>
<td>12 pts (60%)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>1 pts (16.3 %)</td>
<td>2 pts (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 pts (16.3 %)</td>
<td>5 pts (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 pt (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>No Desire 30 pts (69.8%)</td>
<td>15 pts (75%)</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Partial Desire 8 pts (18.6%)</td>
<td>3 pts (15%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 pts (11.6%)</td>
<td>2 pts (10%)</td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td>No Desire 33 pts (76.1%)</td>
<td>16 pts (81%)</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Partial Desire 9 pts (19.6%)</td>
<td>3 pts (14.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 pts (4.3%)</td>
<td>1 pt (4.8%)</td>
<td></td>
</tr>
<tr>
<td>ASIA Scale:</td>
<td>A 40 pts (93%)</td>
<td>19 pts (95%)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>B 0</td>
<td>1 pt (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 3 pts (7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D 0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FAC</td>
<td>0 43 pts (100%)</td>
<td>20 pts (100%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

FAC = Functional Ambulation Category

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Fig. (1): Change in the motor score in the treated and control groups.

Fig. (2): Change of tone in the treated and the control groups (numbers in boxes indicate number of patients).
Fig. (3): Change of ASIA scale in the treated and the control groups (numbers in boxes indicate number of patients).

### Table 3. Recorded side effects in our patients.

<table>
<thead>
<tr>
<th>Recorded side effects</th>
<th>No of patients</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>1/44</td>
<td>Steroid Pulse therapy</td>
</tr>
<tr>
<td>Marked increase in the tone of the abdominal muscles</td>
<td>1/43</td>
<td>Benzodiazepine injection</td>
</tr>
<tr>
<td>Jerky movements</td>
<td>1/43</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>Transient hypertension</td>
<td>3/43</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Excessive sweating below the level of the lesion after the fourth injection</td>
<td>3/43</td>
<td></td>
</tr>
<tr>
<td>Marked increase in spasticity</td>
<td>4/43</td>
<td>Botulinium toxin</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>24/43</td>
<td>Gabapentin, oxycarbamazepine)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Although there is some sort of spontaneous repair after central nervous system injuries, it is incomplete. New spinal circuits may bypass SCI lesions possibly by sprouting of injured corticospinal axons onto spared fibers or an increase in connectivity of long descending propriospinal tracts with lumbar motor neurons. At the subcortical level, the rubrospinal system can reorganize and compensate for much of the function lost after corticospinal injury. However enhanced recovery of function will require a combination of effective and safe therapeutic interventions.

Stem cell transplantation after SCI has several aims: bridging any cysts or cavities, replacing dead
cells by providing new neurons or myelinating cells and creating a favourable environment for axon regeneration.

Our study was performed with the aim of evaluating the value of bone marrow MSCs injected intra-thecally to enhance the repair process in patients with chronic spinal cord injuries.

Forty four patients were included in the treated arm of this study. One case dropped out while the rest continued the study. They were compared to a matched group of patients who received the same rehabilitation program and did not receive any stem cell therapy. Stem cell therapy was given to the treated group, on a monthly basis, for 6 months and follow-up for one year was performed. We used bone marrow MSCs which were shown to have the ability to differentiate into neuronal lineages with some accompanying induction of glial cells.

Reasons for using autologous bone marrow MSCs are avoidance of problems of rejection, overgrowth, disease transmission, and unethical issues. We administered the MSCs intrathecally by lumbar puncture, which is a promising strategy because of its minimal invasiveness, simplicity and low cost.

Enyi et al. found that MSCs survived and engrafted into the spinal cord 2 days after transplantation in rabbits with SCI. They noted that more MSCs were found in the ischemic segment of the spinal cord than in the non-ischemic spinal cord segment after 14 days of MSCs injection. Hind-limb motor function was assessed and there was a significant improvement in movement in the treated rabbits.

Our treated group showed an improvement in the motor power mainly in the form of an increase of one to two points in the motor score. This lead to a limited movement of the hip flexors which, in some subjects, helped to move the lower limbs forward when braces were used in paraplegic patients or when the body weight was externally supported in tetraplegic patients.

There was a significant improvement in trunkal support in both the treated group and the control group. Although the improvement in the treated group was more than that in the control group, the difference was not significant. Trunkal support is particularly important as muscle weakness or abnormal tone in trunk muscles leads to atypical alignment patterns in the trunk, shoulder and pelvic girdles. This misalignment creates an atypical starting position for functional movement that interferes with muscle activation patterns and limits weight transfer between extremities. Consequently, this leads to dysfunction in upper and lower limb control, an increased potential for spinal deformity and contracture, decreased sitting and standing tolerance, postural disturbances and impaired balance function.

We did not find any significant improvement in LTs or PPs in the treated group. This result was similar to that of the control group.

As regards the bladder and bowel control, the noted improvement was in the form of increased desire of micturition and defecation respectively. However, complete control was not reached in any subject. Long term follow up with the use of urodynamic study and anal sphincter electromyography to detect long term reorganization of nerve supply is recommended.

Somatosensory evoked potential studies did not show a significant improvement before and after treatment (p=0.08). This is in agreement with the clinical results which did not find any improvement in LTs, as the tracts mediating LT are the ones responsible for SSEP conduction.

Our study is in accordance with SYKOVA et al., who reported data from 20 patients with complete SCI who received autologous bone marrow mesenchymal cells. Their patients were divided into two groups. The first group (n =6) received MSCs via transfemoral catheterization of a. vertebralis, while the second group (n =14) received MSCs intravenously. They enrolled 7 acute patients who were treated 10–30 days post-SCI and 13 chronic patients who were treated 2–17 months post-SCI. Improvement in motor and/or sensory functions was observed within 3 months in 5 of 7 acute patients and in 1 of 13 chronic patients. The acute patients showed improvement in the ASIA and Frankel scores. The improvement was generally only from the A to B grade. However, in one patient who received MSCs intra-arterially, improvement was seen from B to D in the ASIA scale. Interestingly, improved function was observed in 5 out of 6 patients who received MSCs close to the injury site by catheterization of a. vertebralis, yet we note that 4 of these patients (66%) were those with acute injury.
thus it cannot be determined if this improvement was mainly due to the method of MSC administration or the timing of treatment initiation. They found improvement in median and/or tibial nerves SSEP or motor evoked potentials in four out of six acute patients and in 2 out of 13 chronic patients. Out of the four acute patients, only two showed improvement in the tibial SSEP. This might be explained by the longer intact tracts needed for transmission of tibial SSEPs.

Our study was also in agreement with the small clinical study performed by Park and colleagues on 6 patients with SCI, which showed improvement after treatment with bone marrow MSCs implanted intraspinally within 7 days post injury. Besides direct implantation into the injury site, these authors used a combination of autologous MSCs implantation and subsequent repetitive mobilization of bone marrow cells treated with granulocyte macrophage-colony stimulating factor (GM-CSF). This treatment resulted in improved motor and/or sensory function in 5 out of 6 patients. The difference in the percentage of improved MSC treated subjects between our results and the results of these studies may be attributed to the different methods of implantation, the selected patients and the different times of initiation of MSC therapy after the injury. It is evident that the therapeutic window will play an important role in any type of SCI treatment. There seems to be a similar therapeutic window in humans as in animals, which is up to 3–4 weeks after SCI. In addition, administering the MSCs closer to the injury site, such as through the catheterization of a. vertebralis, or into the cerebrospinal fluid, or even intraspinally at the lesion border, might be important for a better outcome.

In our study, improvement occurred only in traumatic SCI, while myelitic SCI did not show improvement in any of our measured parameters. This may be due to different pathophysiological changes taking place in traumatic and inflammatory SCI. However due to the small myelitic sample (3 subjects) we cannot give a definite conclusion.

The possible mechanisms of improvement seen in our subjects include the MSCs ability to enhance remyelination (unpublished animal study). Sprouting of preexisting axons is an alternative explanation for motor or sensory improvement. Another explanation is that although all the patients were enrolled for a rehabilitation program, those treated with MSCs had greater motivation to interact with the program, thus resulting in improvement of their motor activity.

However, the spinal cord scar formed in chronic SCI is generally believed to be inhibitory. The main components of the scar are astrocytes, type IV collagen, laminin, chondroitin sulphate and proteoglycans. This chronic scar is an important obstacle to the regeneration of the spinal cord. This might explain why our MSCs treated patients did not attain significant functional improvement compared to the control group (p= 0.7).

The use of stem cells is relatively safe. There was not any remarkable decrease in function immediately or after one year of follow up. The recorded side effects in our study included increase in the tone (spasticity) of the muscles (8.7%), and the development of neurogenic pains (52%). Lesions of the spinothalamic pathway alone cannot account for central pain in SCI patients. Neuronal hyperexcitability at the injury or at a higher level might be an important mechanism for pain below the injury level. Sykova et al. studied 11 MSCs treated patients for more than 2 years and did not find any complications following the implantation. Yet, longer follow-up is required to determine the long term safety of MSCs implantation.

In addition to the longer follow-up, we recommend more studies that explore the best dose or duration of treatment of stem cell therapy. Objective assessment of the bladder and bowel function, such as with urodynamical studies and anal sphincter EMG, would be helpful. Imaging of the lesions with MRI after MSCs injections should add more information. Use of markers for neuronal regeneration or remyelination will give more insight into the mechanism of possible recovery.

In conclusion, MSCs therapy is a safe treatment option for patients with traumatic SCI. Further follow-up and research will be needed to adequately define the role of this new treatment modality in SCI patients. We believe more benefits can be accomplished with MSCs therapy when the treatment is performed early within a therapeutic window of 3–4 weeks following injury.

REFERENCES


العلاج بالخلايا الجذعية في علاج الإصابات المزمنة للحبل الشوكي

وجد أن جذع الدماغية لدور في علاج إصابات الحبل الشوكي في التجارب التي أجريت على الحيوان والإنسان. الهدف من هذه الدراسة هو معرفة دور الخلايا الجذعية (الخلايا الجذعية) في تحسين الإصابات المزمنة للحبل الشوكي. تم استخدام عينة من 63 مريض تم تشخيصهم بعد 3-43 يومًا من البداية. تم استخدام عينة مكونة من عينة المرضى الذين تم تشخيصهم بعد 3-43 يومًا من البداية. المرضى الذين تم تشخيصهم بعد 3-43 يومًا من البداية. المرضى الذين تم تشخيصهم بعد 3-43 يومًا من البداية. المرضى الذين تم تشخيصهم بعد 3-43 يومًا من البداية. المرضى الذين تم تشخيصهم بعد 3-43 يومًا من البداية.

قد أظهرت النتائج ما يلي:

- وجدت دراسة واحدة أن الخلايا الجذعية يمكن أن تتحسن في حالة الإصابة المزمنة للحبل الشوكي.
- وجدت دراسة أخرى أن الخلايا الجذعية يمكن أن تتحسن في حالة الإصابة المزمنة للحبل الشوكي.
- وجدت دراسة ثالثة أن الخلايا الجذعية يمكن أن تتحسن في حالة الإصابة المزمنة للحبل الشوكي.
- وجدت دراسة رابعة أن الخلايا الجذعية يمكن أن تتحسن في حالة الإصابة المزمنة للحبل الشوكي.
- وجدت دراسة خامسية أن الخلايا الجذعية يمكن أن تتحسن في حالة الإصابة المزمنة للحبل الشوكي.

لا يوجد خلايا جذعية يمكن أن تتحسن في حالة الإصابة المزمنة للحبل الشوكي.
إلى حد كبير ولكن نحتاج تطبيقات في وقت مبكر من الإصابة ومتتابعة التحسن بواسطة ديناميكالية البول ورسم عضلات لعضلة الشرج وآيضاً دلالات لنمو خلايا عصبية أو خلايا مكونة للمييلين.