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Abstract

Few studies are conducted on the efficacy of human adipose-derived stem cells (ADSCs) in spinal cord injury (SCI) management and electrophysiological changes in the spinal cord. Therefore, the present study aimed to determine the effect of ADSCs on neuropathic pain, motor function recovery, and electrophysiology assessment.

For the purpose of this study, adult male Wistar rats (weight: 140-160 gr, n = 42) were randomly allocated into five groups namely intact animals, sham-operated, SCI non-treated animals, vehicle-treated (culture media), and ADSCs treated groups. One week after clips compression SCI induction, about 1×10⁶ cells were transplanted into the spinal cord. As well, both neuropathic pain (allodynia and hyperalgesia) and motor function were measured weekly. Cavity size, ADSCs survival, and electrophysiology assessments were measured at the end of the eighth week.

The transplantation of ADSCs resulted in a significant improvement in the locomotion of SCI animals (p<0.0001), mechanical allodynia (p<0.0001), cold allodynia (p<0.0001), mechanical hyperalgesia (p<0.0001), and thermal hyperalgesia (p<0.0001). The cavity size was significantly smaller among the ADSCs-treated animals (p <0.0001). The single-unit recording showed that the transplantation of ADSCs decreased wide dynamic range (WDR) in neurons and it evoked potential in response to receiving signals from Aβ (p<0.0001) and Aδ (p=0.003) C-fiber (p<0.0001) neurons. Post-discharge recorded from WDR neurons decreased after the transplantation of ADSCs (p<0.0001) and wind up in the ADSCs-treated group was lower than that of the SCI group (p=0.003).

Our results showed that the transplantation of ADSCs could significantly alleviate neuropathic pain, enhance motor function recovery, and improve electrophysiology findings after SCI.

Keywords: Spinal cord injury; Neuropathic pain; stem cells; Electrophysiological techniques; Wind up

Introduction

Spinal cord injury (SCI) is a destructive disease usually induced by high-energy trauma. Patients with SCI suffer from paralysis, sensory and locomotor dysfunction, urinary incontinence or gastrointestinal disorder⁶. The SCI-related impairment leads to vast personal and societal costs. The global incidence of acute SCI is calculated as almost 10 cases per 100,000 people, resulting in over 700,000 new cases annually detected worldwide⁷. The pathophysiology of SCI has two different phases. Primary injuries cause hemorrhage, the disorder of cell membrane integrity, and neurotransmitter and ion inequality that directly affect neural loss. Secondary injuries include the advanced inflammatory, and ischemic and apoptotic cascade following the initial injury⁸.

Following SCI, neuropathic pain, as a chronic pain presents at the same or below the level of damage⁹. This type of pain is known as one of the most debilitating and all-encompassing conditions leading to the decreased quality of life as well as the incidence of depression and sleep disorders. Of note, Post-SCI neuropathic pain was presented in more than 50% of patients⁹.

Neuropathic pain is a challenging condition and current medical treatments failed to alleviate neuropathic pain because of the heterogeneity of its etiologies and patients’ tolerance to painkillers⁶. Therefore, researchers are attempting to find a new method for the treatment of the neuropathic pain.

Nowadays, stem cells are considered a new therapeutic approach used to manage neuropathic pain. Due to their self-renewal ability, the differentiation capabilities into multiple lineages⁸ as well as the secretion of various neurotropic and anti-inflammatory factors⁷,⁸ stem cells may cause beneficial effects on the management of SCI. Several stem cell-based strategies have been introduced in previous experimental...
and clinical studies. Stem cell transplantation could minimize the development of secondary injuries, increase the survival of spared tissue, and stimulate the regeneration of glial and neuronal precursor cells. The preclinical studies showed that stem cells could release neurotrophic factors and differentiate into neurons; therefore, they can alleviate the neurodegenerative diseases related to neuropathic pain.

There are various sources of stem cells. Mesenchymal stromal/stem cells (MSCs) are a group of heterogeneous multipotent adult stem cells that can be differentiated into neural cells, adipocytes, chondrocytes, endothelial cells, and myocytes. MSCs have therapeutic potential applications for SCI treatment. MSCs transplantation into the injured spinal cord advances axonal regeneration, improves locomotion, and alleviates neuropathic pain. Previous studies have reported that differentiations of bone marrow-derived MSCs (BM-MSCs) into neuronal cells are rare, and their beneficial effects on motor function recovery and axonal regeneration are related to the paracrine activity. Adipose-derived stem cells (ADSCs) are the other source of MSCs. The limited number of studies showed that transplantation of ADSCs could improve spinal cord injury. ADSCs have several advantages such as easier extraction and less painful collection procedure. ADSCs have better tolerance compared to serum-free and hypoxia conditions and oxidative stress. In addition, they showed a higher survival rate when transplanted into the sites of severe SCI under in vivo condition. Transplantation of ADSCs improves locomotor function by enhancing remyelination and the inhibition of glial scar after SCI in mice. ADSCs may differentiate toward a neural lineage and can protect oligodendrocytes in vivo. ADSCs synthesized neurotrophic factors and cytokines/chemokines that cause neuronal survival, axonal regeneration, vascularization, and raised cell survival.

There are few studies on the efficacy of ADSCs on alleviating neuropathic pain after SCI. In addition, the electrophysiological changes after transplantation of ADSCs in spinal cord is still unknown. The present study aimed to assess the efficacy of ADSCs transplantation on SCI-related neuropathic pain and motor function impairment in a rat model of compression injury.

Materials and methods

Study design

Adult male Wistar rats (weight: 140-160 gr, n = 42) were randomly allocated into 5 experimental groups (Table 1). The study protocol was approved by the Iran University of Medical Sciences Ethics Committee (Tehran, Iran) (IR.IUMS.REC.1400.513). The animals were kept under the standard condition (free access to food and water under temperature at + 21 °C and 12-h dark/light cycles). All the stages of this study were approved by the ethics committee of Iran University of Medical Sciences and the code of ethics was obtained.

ADSCs isolation and labeling

Human adipose tissue was elicited from the superficial fat layer of the abdomen of healthy women aged between 25 and 30 years old (after taking consent) who had lipospiare. The isolation methods of ADSCs were presented in detail previously. Briefly, the obtained samples were kept under sterile conditions and then transferred to the laboratory in a sterile dish, digested by collagenase type I (0.1%) and BSA 1%, and centrifuged for 5 min (1200 rpm at room temperature). Thereafter, Red blood cells (RBCs) lysis buffer was added and the second centrifugation was done. Finally, the formed pellet was re-suspended and cultured in DMEM/Ham SF-12 medium, FBS 10%, and penicillin/streptomycin (P/S) 1%. The cultured cells were kept in an incubator (at 37 °C temperature, 5% CO2, and 98% humidity) until the third passage. Before the transplantation, ADSCs were stained via DiI. In summary, 1 × 10⁶ ADSCs were suspended in 1 ml DMEM-F12, including 5 μl DiI (Invitrogen, C-7000, USA) solution (50 μg DiI in 50 μl DMSO) and incubated at 37 °C for 15 min, CO2 5%, humidity 98%, and then at 8 °C for 10 min. After the centrifugation (for 5 min at 1200 rpm) and disposal of the supernatant, the cells were re-suspended in 10 μl DMEM SF-12 for transplantation.

ADSCs flow cytometry

Characterization of ADSCs was performed in the third passage by flow cytometry. CD166 (MABN1785, Merck, Germany), CD44 (CWA-1002, Sigma-Aldrich, USA) and CD73 (MABD122, Merck, Germany) were intended for as positive markers, and CD3 (F0522, Merck, Germany) and CD45 (SAB4700480, Merck, Germany) as negative markers. After trypsinization, ADSCs were centrifuged for 5 min in 3000×g, and then for regaining surface markers, 1 × 10⁶ ADSCs were incubated in DMEM-F12, 10% FBS, and 1% P/S at 37 °C in 5% CO2 for 4 h. In the next phase, the cells were incubated with the conjugated primary antibody for 30 min. Subsequently, the cells were washed with PBS three times and a 500 μl volume aliquot from each sample was removed to a new tube. Flowcytometry was done using Cyflow Space flowcytometer (Sysmex-Partec).

Surgery

After anaesthesia of the animals with ketamine (80 mg/kg, IP) and xylazine (10 mg/kg, IP), they were set in the prone position and their skins were shaved and then cleaned with Povidone-iodine. After putting aside, the muscles and exposing the lamina of the vertebra, laminectomy was made at the T6–T8 level. Thereafter, moderate clips

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Behavioral study</th>
<th>Cavity size</th>
<th>Electrophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Intact animals (n=8)</td>
<td>n=8</td>
<td>n=3</td>
<td>n=5</td>
</tr>
<tr>
<td>Sham</td>
<td>Laminectomy without SCI (n=8)</td>
<td>n=8</td>
<td>n=3</td>
<td>n=5</td>
</tr>
<tr>
<td>SCI</td>
<td>Laminectomy + SCI induction (n=8)</td>
<td>n=8</td>
<td>n=3</td>
<td>n=5</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Laminectomy + SCI + IS transplantation of cell culture media (n=8)</td>
<td>n=8</td>
<td>n=3</td>
<td>n=4</td>
</tr>
<tr>
<td>ADSC</td>
<td>Laminectomy + SCI + IS transplantation of ADSCs (n=10)</td>
<td>n=10</td>
<td>n=3</td>
<td>n=5</td>
</tr>
</tbody>
</table>

TABLE 1. The experimental groups
ADSCs: Adipose-derived stem cells; IS: Intraspinal; SCI: spinal cord injury.
* A rat died during the electrophysiological assessment.
compression model was used (a calibrated aneurysm clips; force=20gr/cm²; for the 60s). Post-surgery care included topical tetracycline and the penicillin G (8 mg/100 gr, IP) for 4 days after surgery, the bladder was emptied twice a day for all the animals. The animals that had a Basso, Beattie, and Bresnahan (BBB) score higher than 3 (at 3-day post-SCI) were removed from the study.

**Stem cell transplantation**

By passing a week after SCI induction, the animals were anesthetized using ketamine and xylazine with the same dose mentioned earlier and their spinal cord was exposed to the T6–T8 area in the same way explained previously. The animals were fixed in a stereotype device and 1 × 10⁶ cells (10 μl volume) were transplanted into the dorsal horn of the spinal cord at two points (0.5 mm rostral and caudal of the injured area at a depth of 1 mm below the dorsal surface). The transplantation was done at a rate of 1 μl/min using a glass micropipette and Hamilton Syringe.

**Behavioral evaluations**

**Locomotion recovery**

Hind limb motor function was evaluated by the BBB locomotor scoring scale (32). Afterward, two observers scored the hind limb motor function blindly and the mean scores were used in the analysis. The locomotor behavior of the animals was evaluated according to hind-limb motor function, weight-bearing, limb concordance, and walking status. The BBB assessment was performed before SCI induction and ADSCs transplantation, and every week until the end of the study (eight weeks follow-up).

**The evaluation of sensory function**

To evaluate the sensory function, four behavioral tests were used, the details of which have been explained in our previous study (29). The pain behavior was assessed before the SCI induction and ADSCs transplantation, and every week until the end of the study (eight weeks follow-up). In summary, mechanical allodynia was measured using the von-Frey test. Moreover, eight filaments of different diameters were used to assess the withdrawal threshold of the animal. A 50% withdrawal threshold was estimated based on the number of animals’ responses. The acetone test was used to estimate cold allodynia. The test was repeated five times for each paw at 1-minute interval, and the number of withdrawals was considered as the response and then recorded as a percentage of the total.

Mechanical hyperalgesia was evaluated (Randall-Selitto test) using an algnesia meter. In this test, mechanical tension was increased on both hind limbs with at least 1-minute gaps and their average was then reported. Heat hyperalgesia was assayed by thermal stimulation of the animal’s hind paw (plantar test). The test was done three times and their average was reported as the animal’s withdrawal latency. For avoiding tissue damage, the device was turned off for 25-second.

**Electrophysiology assessment**

By passing eight weeks from SCI, the animals were sedated using pentobarbital (60 mg/kg), and a laminectomy was performed in the L1–L2 region. The single unit recording was used to assess wide dynamic range (WDR) neurons evoke potentials. The Number of spikes received from Aβ, Aδ, and C-fiber, post-discharge and wind-up phenomenon was calculated after 16 electrical stimuli. The details of the electrophysiology assessment were reported in our previous study (26).

**Histological evaluation**

After eight weeks, the animals were deeply anesthetized and transcardial perfusion was done. Subsequently, the spinal cord was removed and fixated in 4 % paraformaldehyde in 0.1 molar phosphate buffer, pH 7.4, for 24 hours. Thereafter, it was maintained at 10 %, 20 %, and 30 % sucrose solutions for 24 hours, respectively. Serial cross-sectionalizing was prepared (20-μm diameter sections), and Luxol fast blue (LFB) staining was conducted to determine the cavity size. The size of the cavity was divided by the total size of the spinal cord section and then expressed as percentages (n=3 rats; 3 random sections per animal). The obtained data were analyzed using ImageJ software (Wayne Rasband, National Institutes of Health, USA). The survival of the transplanted ADSCs was assessed and photographed by a fluorescent microscope equipped with a camera (Magnification×100). The presence of transplanted Dil labeled cells were confirmed as sharp red spots.

**Statistical analyses**

The analyses were performed in SPSS 22.0 and Graph Pad Prism 6.0 statistical software. Behavioral data were analyzed using repeated-measures ANOVA with a Bonferroni post hoc test. In addition, one-way ANOVA was used to assess the cavity size and electrophysiological assays. The data were presented as mean ± Standard deviation. In all these analyses, p < 0.05 was considered as statistically significant.

**Results:**

**Morphology and flow cytometry**

ADSCs in the third passage were fusiform (Fig. 1 A) and expressed mesenchymal cell surface markers including CD166, CD44, and CD73 but they were negative for CD3, CD34, and CD73 markers (Fig. 1 a-d).

**Effectiveness of ADSCs on motor function recovery**

The transplantation of ADSCs resulted in a significant improvement in the locomotion of SCI animals (df: 32, 296; F = 93.54, p < 0.0001). Three weeks after transplantation of ADSCs some degrees of recovery was observed in the locomotion of animals compared to the SCI group (p < 0.0001). This recovery continued through the eighth week, but it gradually reached a plateau (Figure 2). It is noteworthy, that the motor function score at the end of the study was still lower than healthy animals (p < 0.0001).

**Effectiveness of ADSCs on the mechanical allodynia**

The von-Frey test showed that the SCI has induced mechanical allodynia in animals, the most decrease of the pain threshold has observed in fifth week and this decrease gradually continued until the end of the study (df: 32, 296; F = 26.92; p < 0.0001). Transplantation of ADSCs led to an increase in the paw withdrawal threshold of animals to tactile non-noxious stimuli versus the SCI group (p < 0.0001). Nevertheless, the 50% paw withdrawal threshold of animals was still lower than healthy animals eight weeks after SCI (p = 0.0002) (Fig. 2).

**Effectiveness of ADSCs on the cold allodynia**

SCI resulted in the development of cold allodynia in the studied animals. Peak of cold allodynia was observed at the fifth week of the study (df: 32, 296; F = 10.83, p < 0.0001). However, the transplantation of ADSCs partially reduced the paw withdrawal...
responses of animals to cold stimulus versus the SCI group (p < 0.0001). However, the response rate of animals treated with ADSCs was still higher than the control group (p < 0.0001) (Fig. 2).

**Effectiveness of ADSCs on the mechanical hyperalgesia**

SCI led to some degrees of mechanical hyperalgesia (df: 32, 296; F = 10.75; p < 0.0001). Transplantation of ADSCs resulted in improved mechanical hyperalgesia versus the SCI group (p < 0.0001). At the end of the eighth week, the paw withdrawal threshold of treated animals with ADSCs was still lower than the control group (p = 0.019) (Fig. 2).

**Effectiveness of ADSCs on the thermal hyperalgesia**

After SCI induction, the paw withdrawal threshold of the animals to a painful heat stimulus was gradually decreased (df: 32, 96; F = 15.99 p < 0.0001). Transplantation of ADSCs cells resulted in an increase in the paw withdrawal threshold of the hind limb of treated animals in painful thermal stimulus (p < 0.0001 versus SCI group). However, in the eighth week, this stimulation threshold was lower in the ADSCs group than in the control group (p = 0.002) (Fig. 2).
Fig. 2. Sensory-motor statuses after spinal cord injury (SCI) during 8 weeks follow up. Transplantation of human adipose tissue-derived stem cells (ADSCs) showed significant improvement in motor function score and attenuated allodynia and hyperalgesia. Data are presented as mean±SD. ***, significant difference with intact animals at level of p < 0.0001; **, significant difference with intact animals at level of p < 0.01; *, significant difference with intact animals at level of p < 0.05; ###, significant difference with SCI group at level of p < 0.0001; ##, significant difference to SCI group animals at level of p < 0.01; #, significant difference with SCI group at level of p < 0.05.
**Fig 3.** Light microscopic evaluation of cavity size of the animals after spinal cord injury (SCI) after 8 weeks follow up (×10). Transplantation of human adipose tissue-derived stem cells (ADSCs) significantly decreased cavity size after SCI. Data are presented as mean±SD. ###, significant difference with SCI group at level of p < 0.0001.
Fig. 4. Fluorescence microscopic evaluation of Dil labeled human adipose tissue-derived stem cells (ADSCs) (×100). Host cells are stained by 4',6-diamidino-2-phenylindole (DAPI). Dil positive cells (transplanted cells) in the lesion area after 8 weeks were confirmed as sharp red spots (white arrow).

Cavity size and ADSCs survival

Eight weeks after SCI a large cavity was observed in the spinal cord (df: 2, 26; F = 43.96; p < 0.0001). The cavity size was significantly smaller in ADSCs treated animals (p < 0.0001). Cavity size in the SCI group was 41.8 ± 7.1% and in the ADSCs group was 11.5 ± 1.9% (Fig. 3). Fluorescence microscope assay showed that ADSCs cells were still observed at the end of week 8 (Fig. 4).

Electrophysiological findings

The single-unit recording showed that after SCI evoked potentials recorded from WDR neurons were significantly increased. Eight weeks after SCI, WDR neurons responded to signals received from Aβ (df: 4, 18; F = 44.49; p < 0.0001), Aδ (df: 4, 18; F = 18.97; p < 0.0001), and C-fiber (df: 4, 18; F = 44.49; p < 0.0001) significantly increased compared to the control group. In addition, post-discharge (df: 4, 18; F = 91.95; p < 0.0001) and wind-up phenomenon (df: 4, 18; F = 25.47; p < 0.0001) was significantly higher in SCI animals.

The Transplantation of ADSCs decreased WDR neurons evoked potential in response to receiving signals from Aβ (p < 0.0001 versus SCI group) and Aδ (p = 0.003) neurons and reached the level of the control group (p > 0.99). The response of WDR neurons to the C-fiber impulses also decreased after ADSCs transplantation (p < 0.0001 versus SCI group), but was higher compared to the control group (p = 0.033).

Post-discharge recorded from WDR neurons decreased after transplantation of ADSCs (p < 0.0001 versus SCI group), which level was still higher than the control group (p = 0.005). Finally, wind up in the ADSCs treated group was lower than the SCI group (p = 0.003). However, the level of wind up in the ADSCs did not reach the level of the control group (p = 0.044) (Fig. 5).

Discussion

Our results showed that intraspinal transplantation of ADSCs significantly improved neuropathic pain and motor function recovery after SCI. ADSCs could decrease the cavity size and survive 8 weeks after SCI. Electrophysiological findings showed that the transplantation of ADSCs decreased evoked response of the WDR to Aβ, Aδ, and C fiber impulses, and improved post-discharge and wind-up phenomena.

Chronic pains such as neuropathic pain caused significant and complicated plasticity within the injured neurons that could alter gene expression, the function of ion channel and receptors in neurons, microglia, and glia. These changes could result in functional rewiring, sensitization of the neural pathways, neuronal excitability[38]. Under normal condition, WDR neurons (second order neurons) are relatively silent and or show several spontaneous action potentials, but after repeated stimulation or nerve damage associated neuropathic pain, they start spontaneous firing increasingly; therefore, they become sensitive to stimuli. So, due to this reason, the discharging and winding up of these nerves increase when nerve is damaged. Therefore, WDR neurons give a sensitized response to a low-intensity stimulus (allodynia), and an increased response to high-intensity stimuli (hyperalgesia)[39]. WDR neurons cause the plasticity of synapses[40] and flexibility in the neuron's response and this function can be considered as the benefit of the organism. However, high activity of WDR neuron can induce chronic pain[41]. To confirm the above-mentioned studies, the result of our electrophysiology assay showed that following SCI, the firing rates of Aβ, Aδ, C fibers increased. ADSC therapy could decrease the firing rate and reduce the wind-up phenomenon. Our behavioral assessment confirmed the electrophysiology results.

In 2016, Yousefifard et al. conducted an experimental study to evaluate the effect of BM-MSC and UC-MSC on SCI-related neuropathic pain. In this study, an 8-week follow-up showed that both BM-MSC and UC-MSC could reduce allodynia and hyperalgesia[26]. In another study, Sarveazad et al. showed that ADSCs reduced the expression of GSK3β (as inflammatory and apoptosis mediator in the CNS which prevents axonal regeneration), and interleukin-6 and also increased GDNF expression and the expression of type I and 2 GABA receptors. The paracrine activity of ADSCs can improve the survival of host motor and sensory neurons, neurogenesis, axonal regeneration, and myelination[28]. These molecular changes might be the reason for locomotion improvement and alleviating neuropathic pain. We showed that the ADSC could survive at least 8 weeks post-SCI. Therefore, paracrine activity of ADSCs could remain for a long time.
Fig. 5. Single unit recording 8 weeks after spinal cord injury (SCI). Transplantation of human adipose tissue-derived stem cells (ADSCs) showed significant decreases in evoked potential of the WDR neurons to receive impales from Aβ neurons, Aδ, and C fibers, post-discharge response, and wind up. Data are presented as mean±SD. ***, significant difference with intact animals at level of p < 0.0001; **, significant difference with intact animals at level of p < 0.01; *, significant difference with intact animals at level of p < 0.05; ###, significant difference with SCI group at level of p < 0.0001; ##, significant difference to SCI group animals at level of p < 0.01.
In the current study, we found that transplantation of ADSCs improved locomotion of SCI animals. Two independent research groups showed that ADSCs could differentiate into motor neuron-like and neural tissue cells, they could protect oligodendrocytes in vivo and decrease remyelination in the injured spinal cord. ADSCs have a high ability to be differentiated into functional Schwann cells. However, recent studies showed that the beneficial role of ADSCs has been mediated via its paracrine activities. ADSCs could secrete growth factors and anti-inflammatory cytokines, which could improve host cell axonal regeneration and stimulate angiogenesis, and finally enhance motor function and reduce neuropathic pain symptoms. These cells secret brain microvascular neurotrophic factor (BDNF) expression, nerve growth factor (NGF), and derived neurotrophic glial factor (GDNF) and nitrous oxide, IL-4, IL-6, and IL-1 receptors antagonist, which can potentially induce neuro-regeneration, promote angiogenesis, decrease inflammation, trigger antiapoptotic processes at the injury site.

Gao et al. showed that ADSCs could be differentiated into electrically-active motorneurons. After transplantation of ADSCs to the damaged spinal cord, a considerable motor recovery was observed. These cells survived after 8 weeks and showed neuronal phenotype and they are involved in the regeneration of damaged circuitry by optimizing the microenvironment and also by balancing the inflammatory responses. Our findings are compatible with the Gao et al.’s study. We showed that ADSCs survived eight weeks after SCI and it could modulate the electrical conduction via ascending pathways in spinal cord.

Therefore, there are three mechanisms proposed for ADSCs therapy in improving SCI-related complication as follows: 1) ADSCs have a high ability to be differentiated into targeted cells and regenerate the injured area; 2) they have paracrine functions and secrete many cytokines and growth factors to neighbor cells, which lead to vascularization and cellular proliferation in damaged organs; and 3) MSCs have immunomodulatory properties. Therefore, they can decrease inflammation in injured area.

Recently, ADSCs have been applied to treat neuropathic facial pain in eight patients. These cells were injected into the trigeminal nerve. After 6 months, the patients’ visual analog pain score reached 3.2, and decreased the need for gabapentin administration with no serious complications. In another study, stem cells of autologous adipose tissue were used to treat the pudendal neuralgic disease. The finding showed that 66.6% of these patients experienced a significant reduction of pain score after 12 months of their treatment. ADSCs could alleviate neuropathic pain via decreasing the IL-1β level (the pro-inflammatory cytokine) and enhancing the IL-10 expression in the damaged nerve. Some experimental and clinical studies have also shown that co-administration of ADSC and other therapeutic strategies such as laser therapy enhanced ADSCs efficacy. This kind of treatment might improve the survival and paracrine activity of the ADSCs.

Limitation

Although studies reported no side effects for ADSCs, we need more evidences before performing translational studies. The cultured ADSCs should be evaluated for their toxicity and tumorigenesis. We did not assess the differentiation capability of ADSCs into neural cells. There are several studies, which have shown the efficacy of ADSCs could mediate by its paracrine activity. Therefore, the evaluation of differential properties of ADSCs into neural tissue seems unnecessary.

Conclusion

The use of ADSCs can be effective on reducing the complications of spinal cord injury. The results showed that the decreased neuropathic pain (allodynia and hyperalgesia) the ability to move in order to be improved. Also, tissue recovery such as cavity size reduction was observed after ADSC injection.

References


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Statements and Declarations

Competing interests

The authors declared that they have no competing interests.

Ethics approval

Experimental research protocol on animals was approved by the ethics committee of the Iran University of Medical Sciences (IR.IUMS.REC.1400.513).

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Availability of data and material

Data are however available from the corresponding author upon reasonable request.

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