REVIEW ARTICLE

GMJ.2022;11:e2541
www.gmj.ir

Received 2022-08-10
Revised 2022-09-02
Accepted 2022-09-07

The Therapeutic Effect of Mesenchymal Stem Cells in Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is an injury of the spine that could be life-threatening and lead to partial or complete loss of autonomic, sensory, and motor function below the injured area. Surgery decompression and steroid injection are the current treatments for SCI, but neither is particularly effective, and there is a growing demand for a more potent treatment. Mesenchymal stem cells (MSCs) are novel therapeutic agents that were used in different inflammatory diseases. These cells have immunomodulatory and regenerative properties which make them a promising candidate for neurological disorders such as SCI. MSCs are easily expandable in vitro and have the capacity for multilineage differentiation. These cells, which can be derived from adipose tissue, bone marrow (BM), Wharton jelly, or umbilical cord, have immunomodulatory and paracrine capabilities. They can release a variety of cytokines and other substances that suppress the growth of B cells, T cells, and natural killer cells (NKCs) as well as alter the activity of dendritic cells (DCs). In this study, we reviewed clinical studies that showed the effects of MSCs from different sources in the SCI.

[GMJ.2022;11:e2541] DOI:10.31661/gmj.v11i.2541

Keywords: Bone Marrow; Mesenchymal Stem Cells; Spinal Cord Injuries; Umbilical Cord; Adipose Tissue

Introduction

Spinal cord injury (SCI) is a clinical issue with significant socioeconomic consequences. The SCI damage the spinal cord (SC), it is a catastrophic event that results in morphological and physiological abnormalities as well as biomechanical and functional impairments in patients [1, 2]. The acute and chronic inflammatory processes brought on by this illness may have short- or long-term effects, such as paraplegia, quadriplegia, or even death [2, 3]. Following a basic mechanical injury to the spinal cord tissue, several secondary processes involving different patho-

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logical reactions speed up the massive cell loss, release of cytotoxic agents, and cystic cavitation [4, 5]. Additionally, the hostile environment and the abundant extracellular matrices (glial scarring) created by active astrocytes significantly restrict cell migration and axonal regrowth [6]. However, situations that cause SCI (such as traffic accidents, criminal activity, or secondary causes (such as degenerative diseases and tumors)) can be prevented, but the main challenge that scientists face is the lack of the gold-standard. Most post-traumatic nervous system degeneration is caused by numerous distinct molecular mechanisms, including apoptosis, blood-brain barrier (BBB) dysfunction, free radicals, disconnection of normal nerve pathways, neuronal death, inflammation, ionic dysregulation, lipid peroxidation, and necrosis followed by cavitation and retrograde degeneration., Early surgical decompression along with spinal fixation after traumatic SCI appears to be crucial in minimizing subsequent damage between 8 and 24 hours after injury [7, 8].

The two most common treatments for SCI are surgery decompression and steroid injection, but neither is particularly effective, and there is a growing demand for a more potent treatment [9]. Stem cell transplantation as a novel therapeutic method has generated growing interest due to its encouraging outcomes in neurological recovery in SCI, [10-13]. Among the stem cells, mesenchymal stem cells (MSCs) are considered a promising treatment option, since they can exert paracrine and autocrine effects. These effects can encourage cell proliferation and differentiation. Also, these cells have immunomodulatory effects which affect the host's microenvironment [14-16]. The therapeutic abilities of MSCs are wide and include neuroprotection following glutamate excitotoxicity [17, 18], the production of neurotrophic factors [19, 20], a decrease in reactive oxygen species, proinflammatory cytokines, and stress-related protein levels [21, 22], the polarization of M1 macrophages to the M2 phenotype [23], and the capacity to generate large quantities of the exosome. Additionally, MSCs support axonal development by encouraging angiogenesis and remyelination and prevention of apoptosis. MSCs exert these effects through their trophic and anti-inflammatory factors [24].

Because MSCs have so many benefits over many other kinds of stem cells, MSCs are highly intriguing and have little responsiveness toward the host as well as a low risk of creating a tumor [25]. In this study, we reviewed clinical studies that showed the effects of MSCs from different sources in the SCI.

Spinal cord injury

Injury to the spine is a neurological condition that can be fatal and results in either partial or complete loss of autonomic, sensory, and motor function below the injured area [26]. Spinal cord mechanical insult occurs when the spinal cord is disrupted as a result of compression, contusion, or transaction, and causes the initial primary injury [27, 28]. Minutes after the mechanical injury, secondary processes emerge, manifesting as ischemia, ionic alterations, thrombosis, edema, apoptotic and necrotic cell death, lipid peroxidation, excitotoxicity, and production of free radicals. Together, they all contribute to inflammation and unchecked immunological response. Understanding how continuing secondary mechanisms impact both the cells that survive in the main damage site and those in the surrounding tissue will help prevent the lesion from spreading into nearby parts of the spinal cord in the rostrocaudal and caudal directions [29]. Additionally, functional recovery is ultimately impossible due to advanced axonal degeneration, tissue necrosis, cavity formation, and scarring [30, 31].

Mesenchymal stem cells

Mesenchymal stem/stromal cells (MSCs) can easily be extracted from different tissues and have a tremendous capacity for growth [32]. They make up 0.001-0.01

percent of all nucleated bone marrow cells and are found in the majority of connective tissues, such as perivascular tissue, umbilical cord blood, adipose tissue, and bone marrow [33, 34]. MSCs have the potential to differentiate into adipocytes, chondroblasts, and osteoblasts [35, 36]. The International Society for Cellular Therapy (ISCT) established the least standards for MSCs in 2006. These standards include the plastic adhesion to the flask in the culture conditions, expressing or being positive for molecules such as CD73, CD105, and CD90, and the absence of surface markers including CD34, CD45, CD79alpha, or CD19, CD14, or CD11b, and HLA-DR. These cells can also differentiate into chondroblasts, adipocytes, and osteoblasts in vitro [37]. In clinical trials, MSCs are commonly employed, due to their biological features, such as their anti-inflammatory capabilities, immunomodulation, neuroprotection, capacity for multilineage differentiation, and encouragement of tissue repair [38, 39]. It was theorized that MSCs would settle in injured tissues where they would grow and replace damaged cells. According to several studies, MSCs can migrate selectively and exert homing abilities on different organs [40, 41]. MSCs have various ligands and receptors that direct them into damaged tissues [42]. This mechanism is not affected by the route of administration. Furthermore, MSCs have a strong chemotactic activity, which promotes the recruitment of other cells. Fibroblasts speed up integrin expression, proliferation, and migration in response to MSC secretome [43, 44]. Similar to this, after receiving MSC stimulation following an in vitro microbial assault, neutrophils enhance their migratory rate and immune response [45, 46]. MSCs have been shown to be able to control the immune response in a cell-to-cell manner and also the production of several mediators like proapoptotic and antiapoptotic molecules, enzymes, prostaglandins, and cytokines [47, 48]. These cells change the macrophages reprogramming and start the alteration of these cells from the M1 phenotype to M2, which consequently increases the M2 macrophages and decreases the M1 phenotype. Additionally, it has been shown that the administration of MSCs decreases the production of pro-inflammatory cytokines like tumor necrosis factor (TNF), interleukin-12 (IL-12), IL-1β, and IL-6 in animal models of ulcerative colitis and peritonitis [49, 50].

Adipose tissue MSCs (ATMSCs) in the SCI

Currently, fat cells are also taken into consideration because BM isolation needs specialized assistance and has some donor restrictions. They are easier to obtain through surgical procedures like liposuction [51]. There are a few advantages and distinctions between ATMSCs and BMSCs. Although BMSCs have different multilineage and proliferation abilities, they are similar in expressing surface markers [52]. It should be noted that conflicting statistics have been reported in relevant studies. According to previous studies, ATMSCs are more effective than BMSCs, while BMSCs outperform ATMSCs [53]. As a result of differences between ATMSCs and BMSCs in terms of apoptosis, chemokine receptor expression, and cytokine release [54, 55], different results may be achieved. Additionally, ATMSCs exhibit increased proliferative activity and have the capacity to secrete greater amounts of IL-8, Vascular Endothelial Growth Factor D (VEGF-D), and Insulin-like growth factor 1 (IGF-1) [55]. While BMSCs release Hepatic Growth Factor (HGF), stem cell-derived factor-1, Nerve growth factor (NGF), Basic fibroblast growth factor (bFGF), angiogenin, and VEGF-A equivalent to ATMSC levels, they proliferate more slowly and exhibit higher levels of osteogenesis and chondrogenesis [56]. These findings have led to a preference for ATMSCs in the stimulation of angiogenesis. To select stem cells for a particular clinical trial, it is important to consider their variety of biological activities and immunomodulatory qualities [57, 58]. In a clinical trial using intrathecal implantation of autologous ATMSCs in patients with SCI

at the lumbar thoracic, and cervical levels moderate improvements were revealed in sensory scores and American Spinal Injury Association Impairment (ASIA) motor at eight months of follow-up. Three patients experienced negative side effects, including urinary tract infection (UTI), vomiting, nausea, and headache [59]. Similar to this, a case report from a phase I trial claimed that intrathecal autologous ATMSC distribution was possible, safe, and showed evidence of improving neurological state [60]. The inflammatory suppression effect of ATMSC is mediated by inhibiting the invasion of ED1 macrophages and reducing neurogenic locus notch homolog protein 1 (Notch 1) signaling [57, 61]. Delivery of ATMSCs soon after a contusion in a mouse model of SCI reduced neuronal death and enhanced mobility. Other mechanisms, such as the factors involved in Notch1 signaling, including RBP-JK, NICD, and Jagged1, may be in charge of this positive effect as administrated ATMSCs do not develop into the brain or glial cells [57].

Bone-marrow MSCs (BMSCs) in the SCI

In both experimental and clinical trials, BMSCs were the first cells utilized to treat traumatic injury [62]. In primary studies based on thoracic spinal cord injury and administration of BMSC in rat animal models, it was revealed that autonomic, sensory, and motor properties were partially improved [63]. It should be noted that similar positive effects were seen when BMSCs were given locally, intrathecally, or systemically into the spinal cord cavity [64-66]. In a study, it was shown that intravenous (IV) administration of BMSCs one week after the injury in a rat model of SCI, significantly improved the motor and sensory assessments in behavioral tests [67]. Magnetic resonance imaging (MRI) was also applied in those investigations to track the development of administrated cells in the SCI [68, 69]. Before being transplanted into the SCI animal model, adult BMSCs were grown with superparamagnetic iron-oxide nanoparticles. The MRI imaging of SCI showed the BMSCs as hypointense signals that persisted for longer than 4 weeks and also confirmed it at the lesion site [69, 70]. Tissue loss, such as spinal atrophy and cavity formation, in chronic SCI leads to a sustained functional impairment. To treat spinal cord injuries, it is consequently necessary to implant a functionalized scaffold to fill any spinal cavities. Patients with chronic SCI showed some improvement in their motor and sensory function following the implantation of hydrogel seeded with BMSCs in vitro [71]. Several phases I/II clinical trials using autologous and allogeneic BMSCs or mononuclear fractions in patients with acute, subacute, or chronic SCI were started as a result of these encouraging preclinical investigations. In conclusion, these clinical trials' findings showed that BMSCs are risk-free and free of side effects. All mononuclear cells from BM were employed in one of the early experiments [62]. Numerous patients showed recovery of motor-evoked potentials and somatosensory evoked potentials, and partial improvement in the ASIA score When treated during the acute or subacute period. The clinicaltrial.gov website offers a summary of these trials. Subsequently, several phases I/II clinical studies were initiated in Switzerland, Chile, Brazil, China, Egypt, India, Japan, and Korea. These research findings are modest but encouraging [72, 73]. However, bigger populations of patients are necessary before making any practical statements, despite the encouraging findings that were attained [74].

Umbilical cord MSCs (UCMSCs) in the SCI

The limited efficiency of the adult stem in laboratory models of SCI may contribute to the eventual failure of clinical practices. Due to this, much work has gone into discovering a stem cell source that is more similar to an embryo. As a result, umbilical cord Wharton's jelly-derived MSCs (WJMSCs) have shown therapeutic promise [75]. These cells have no

tumorigenicity, decreased immunogenicity, and increased proliferation, giving them more embryonic-like characteristics [76, 77]. In addition to stimulating neurogenesis and angiogenesis, they release large quantities of Glial Cell Line-Derived Neurotrophic Factor (GDNF), bFGF, NGF, the neurotrophic factors Neurotrophin-3 (NT-3), NT-4, as well as other molecules linked to neuroprotection [75]. In a recent study, the repeated intrathecal administration of WJMSCs into an SCI rat model revealed the spinal cord's potentiated regeneration in a dose-dependent manner. Administration of WJMSCs in higher doses lowered the glial scar, protected the nerve tissue, and increased the amount of Growth Associated Protein 43 (GAP43)-positive fibers, according to histochemistry in particular [78].

Future directions

All inclusive, the use of MSCs in SCI seems to be safe and there is little evidence of serious adverse responses. However, the positive findings from the preclinical trials, have not yet been confirmed by the results of the clinical trials. Preclinical studies are difficult to replicate in human studies, as they typically use particular animal models with defined protocols, established therapies, and the timing of the transplanting. This could be the cause of the problem. These factors can be easily controlled in the environment of animal experiments, however, in clinical trials, these factors are dependent on the emergency setting, the traumatic incident, and chance. Phase III clinical trials are also very underrepresented for both ethical and budgetary reasons. One of these phase III clinical trials revealed that therapeutic efficacy is modest and constrained [79]. In particular, the best therapy protocols should consider different parameters such as the route of administration, amount of cells, and the time of administration for its clinical application in the SCI. However, as a result of the technological revolution, researchers are currently looking into enhancing cell survival and tissue repair by the use of MSCs in conjunction with novel biomaterials [80]. In this regard, the therapeutic impact of MSC administration in conjunction with a collagen scaffold could enhance cell adhesion and migration [81]. The patients' damage status shifted from ASIA A to ASIA C after the transplant,, and their motor, sensory, and urination functions significantly improved [82]. The idea of integrating MSCs with hydrogels is very appealing due to their capacity to be loaded with specific medications that may be further released in a controlled manner and their capacity to be injected with little invasion [83]. Further research is necessary to completely understand and increase MSCs' capacity to stimulate the production of neuroprotective, immunomodulating, and neurotrophic factors to enhance therapeutic results [84].

Conclusion

MSC treatment is an attractive area of study attempting to deal with the burden of SCI. The safety and efficacy of different sources of MSCs have been shown in previous SCI studies. However, most of these studies are preclinical studies. clinical studies should also be done for a better understanding of MSCs' effects on humans. To improve the efficacy of cell therapy, preclinical and clinical studies must communicate better and adopt a back-and-forth strategy. However, stem cell therapy in SCI is still an experimental treatment that should be investigated and should be provided to the patient without charge. It may also be used in combination with other therapies. In addition, patients should be informed of the subpar clinical results shown thus far in clinical trials to avoid having unrealistic expectations and suffering from major psychological effects if significant results are not seen.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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