Review Article

Int Neurourol J 2020;24(Suppl 1):S3-10
https://doi.org/10.5213/inj.2040150.075
pISSN 2093-4777 · eISSN 2093-6931

INTERNATIONAL NEUROUROLOGY JOURNAL
INJ
OPEN ACCESS

Stem Cell Therapy for Neurogenic Bladder After Spinal Cord Injury: Clinically Possible?

Su Jin Kim[1], Young Sam Cho[2], Jong Mok Park[3], Young Gil Na[3], Khae Hawn Kim[4]

[1]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea
[2]Department of Urology, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Urology, Chungnam National University Sejong Hospital, Chungnam National University College of Medicine, Sejong, Korea
[4]Department of Urology, Gachon University Gil Medical Center, Gachon University of School of Medicine, Incheon, Korea

Neurogenic bladder (NB) after spinal cord injury (SCI) is a common complication that inhibits normal daily activities and reduces the quality of life. Regrettably, the current therapeutic methods for NB are inadequate. Therefore, numerous studies have been conducted to develop new treatments for NB associated with SCI. Moreover, a myriad of preclinical and clinical trials on the effects and safety of stem cell therapy in patients with SCI have been performed, and several studies have demonstrated improvements in urodynamic parameters, as well as in sensory and motor function, after stem cell therapy. These results are promising; however, further high-quality clinical studies are necessary to compensate for a lack of randomized trials, the modest number of participants, variation in the types of stem cells used, and inconsistency in routes of administration.

Keywords: Urinary bladder; Neurogenic; Spinal cord injury; Stem cells, Clinical trials

- **Fund/Grant Support:** This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2018R1D1A3B07048492).
- **Conflict of Interest:** SJK, YSC, and KHK, members of the Editorial Board of *International Neurourology Journal*, are the authors of this article. However, they played no role whatsoever in the editorial evaluation of this article or the decision to publish it. Except for that, no potential conflict of interest relevant to this article was reported.

INTRODUCTION

Regenerative medicine provides a valuable therapeutic framework for remedying remedy difficult-to-treat diseases and impaired tissue. The term "regenerative medicine" was first used by Kaiser in 1992 [1]. Cell-based therapy and tissue engineering are the two most significant components of regenerative medicine, and each of them can be applied independently or in combination to generate synergistic effects [2]. In the history of regenerative medicine in urology, Atala et al. [3,4] showed promising results by implanting a tissue-engineered bladder and urethra using autologous cells and scaffolds in humans for the first time. Since then, extensive research has investigated the possibility of using stem cells for therapeutic purposes in various difficult-to-treat urologic diseases such as incontinence, neurogenic bladder (NB), erectile dysfunction, and interstitial cystitis/bladder pain syndrome [5].

Stem cell therapy has been invaluable in the treatment of numerous serious diseases that cannot be adequately treated with existing therapeutic modalities. Therefore, NB associated with central nervous injury or dysfunction is an optimal candidate for stem cell therapy because it is challenging to promote the

Corresponding author: Khae Hawn Kim https://orcid.org/0000-0002-7045-8004
Department of Urology, Gachon University School of Medicine, Gil Medical Center, 21 Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Korea
E-mail: kimcho99@gilhospital.com / Tel: +82-32-460-3334 / Fax: +82-32-460-8340
Submitted: April 1, 2020 / **Accepted after revision:** May 9, 2020

recovery of injuries or degenerative changes in the central nervous system [6-8]. Disability induced by spinal cord injury (SCI) is a serious problem that impacts quality of life, and its prevalence is noteworthy, although the exact incidence has not been determined. In aging societies, falls are common among elderly individuals, which has contributed to an increasing incidence of SCI [9,10]. One of the most common problems in SCI patients is NB; however, the current medical and surgical treatment of NB focuses only on modulating the function of the bladder, not on promoting recovery of the SCI [11,12]. In addition, the therapeutic outcome of NB treatment is generally insufficient because the SCI is often permanent. Thus, neuronal regeneration using stem cell therapy may contribute to the restoration of functional impairment after SCI.

MECHANISM OF STEM CELL THERAPY IN NEURAL REGENERATION AFTER SPINAL CORD INJURY

At present, the Wnt/β-catenin signaling pathway, the Rho/Rock signaling pathway, the Notch signaling pathway, and the JAK-STAT3 signaling pathway have been considered as possible signaling pathways associated with neural regeneration after stem cell therapy. After SCI activation of the Wnt/β-catenin signaling pathway promotes neural regeneration, while the Rho/Rock signaling pathway, the Notch signaling pathway, and the JAK-STAT3 signaling pathway inhibit neural regeneration. The Wnt/β-catenin signaling pathway contributes to the development of the nervous system and is activated in the early period after SCI and subsequently decreases with time. Wnt expression increases rapidly in the acute phase of SCI. Therefore, increased expression of Wnt plays a role in recruiting endogenous neural stem cells and in restoring damaged neural tissue [13-20]. Thus, up- or down-regulation of these signaling pathways influences the neural differentiation of stem cells.

To improve the role of stem cells in repairing damaged tissue, the microenvironmental balance around stem cells is also important. The extracellular matrix (ECM), cytokines, and tissue-specific cells modulate the microenvironment, and an imbalance of these components inhibits neural regeneration. The ECM is a 3-dimensional network that shapes the central nervous system, and breakdown of the ECM after SCI influences neuronal and nonneuronal cell migration, communication, and survival, which are important for recovery from SCI. Therefore, ensuring an adequate ECM for the damaged spinal cord is a therapeutic approach that aims to provide a proper environment for repair after SCI [21]. Several studies have shown a synergistic effect after combined treatment with biocompatible scaffolds and stem cells [22-24]. Moreover, the paracrine effect of stem cells promotes neural regeneration by regulating neurotrophic factors, cytokines, and chemokines [25].

PRECLINICAL STEM CELL THERAPY FOR THE TREATMENT OF SPINAL CORD INJURY

Multiple preclinical studies have investigated the use of various types of stem cells after SCI, evaluating the roles of mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and neural stem cells in morphological and functional recovery after SCI. Many studies have investigated stem cell therapy with MSC have been performed because MSCs because MSCs have considerable potential for differentiation and anti-inflammatory and immunomodulatory properties [26]. MSCs can be isolated from various tissues, such as the bone marrow, umbilical cord, adipose tissue, and oral mucosa. All types of MSCs have been shown to lead to neural regeneration in a SCI animal model induced by spinal cord transection and contusion. Moreover, therapeutic effects of MSCs have been observed in both the acute and chronic phases after SCI. Regarding the route of administration, direct injection to the injured area and intravenous or intrathecal administration of MSCs have led to improved neural regeneration [27-32]. Bone marrow mesenchymal stem cells (BM-MSC) is low immunogenicity compared with MSCs from other tissue. However, considerable pain that occurs during the process of obtaining BM-MSC from bone marrow is an issue. In contrast, adipose-derived stem cells (ADSCs) have the advantage of being readily obtainable from adipose tissue. Therefore, the patient experiences less pain than when BM-MSCs are used.

Many studies have investigated the use of iPSCs because iPSCs derived from autologous somatic cells have similar characteristics to embryonic stem cells, therevy circumventing ethical issues [33]. Several studies have shown autologous iPSC-derived neural precursor cells exerted effects on neural regeneration through remyelination after SCI [34-36]. However, iPSCs have a higher rate of tumorigenicity due to the epigenetic memory of the original somatic cells and reprogramming. Neural stem cells are obtained from the brain (lateral ventricle, dentate gyrus of the hippocampus) and the central canal of the spinal cord. Neural stem cells can differentiate into neurons, as-

Table 1. Completed clinical trials that reported results (http://clinicaltrials.gov/)

Identifier	Clinical trial phase	Type of SCI	No. of patients	Age (yr), range	Cell type	Delivery method	Efficacy	Safety
NCT01325103 [39]	Phase 1	Thoracic or lumbar traumatic SCI (ASIA grade A)	14	18–65	Autologous BM-MSC	Intralesional injection after laminectomy and decompression of the spinal lesion area	Variably enhanced sensitivity below the injury area was observed. 8 patients: improvement of lower limb motor function, 7 patients: improvement of AIS, 3 patients: improvement of neuropathic pain	14 Patients: discharge within 48 hours after surgery, 1: cerebrospinal leak related to surgery, no severe adverse events
NCT02482194 [40]	Phase 1	Chronic and subacute SCI	9	18–50	Autologous BM-MSCs	Intrathecal injection	At 1 year after treatment, no alteration in the hyperintense signal and no formation of ectopic tissue	No severe adverse event, 1 patient: severe headache, 2 patients: nonspecific tingling sensation
NCT01909154	Phase 1	Chronic paraplegia (ASIA grade A)	9	18–50	Autologous BM-MSCs	Intrathecal injection (second injection at 3 months after the first injection)	Sensory recovery, improvement of chronic pain, presence of SSEPs	No severe adverse events, nausea, urinary tract infection, back pain, thoracic pain, muscle contracture, myalgia, headache
NCT00816803 [41]	Phase1/2	Chromic SCI with thoracic spinal trauma	70	10–36	Autologous BM-MSCs with physiotherapy (n = 50), standard rehabilitative therapy with physiotherapy (n = 20)	Intrathecal injection	Autologous BM-MSCs with physiotherapy group: 17 patients showed improvement of the ASIA score, 23 patients showed improvement of motor function	Headaches, mild pain
NCT01274975 [42]	Phase 1	Traumatic SCI (ASIA grade A or B)	8	19–60	Autologous ADSCs	Intravenous infusion	MRI at 12 weeks after therapy showed a reduction of injured lesions without significance. Conversion from ASIA A to ASIA C and improvement of motor and sensory function were noted in 1 patient	No severe adverse events
NCT01393977 [43]	Phase 3	Thoracolumbar SCI	34	20–50	UC-MSC transplantation group, rehabilitation therapy group, control group	Intrathecal injection	Seven of 10 patients treated with UC-MSCs showed significant improvement of motor function	Radiating neuralgia after UC-MSC transplantation; improvement within 24 hours

SCI, spinal cord injury; ASIA, American Spinal Injury Association; BM-MSCs, bone marrow stem cells; AIS, Association Impairment Scale; SSEP, somatosensory evoked potential; ADSCs, adipose-derived mesenchymal stem cells; MRI, magnetic resonance imaging; UC-MSCs, umbilical cord mesenchymal stem cells.

trocytes, and oligodendrocytes in the nervous system [37]. Previous studies of neural stem cells showed axonal regeneration at the injured area and functional recovery [38].

CLINICAL TRIALS OF STEM CELL THERAPY AFTER SPINAL CORD INJURY

A considerable number of clinical trials that have evaluated the effects and safety of stem cell therapy in SCI patients on the basis of preclinical research. Therefore, a review of clinical trials registered on ClinicalTrials.gov was performed to evaluate the outcomes of stem cell therapy in SCI patients. In total, 30 clinical trials were identified (complete: n = 18 and ongoing: n = 12), excluding withdrawn and terminated studies. Six of the 18 completed studies reported the results of the trials (Table 1). The completed clinical trials were phase 1 or 2 studies, and types of stem cells were autologous BM-MSCs, autologous ADSCs, and umbilical cord mesenchymal stem cells (UC-MSCs) [39-43]. There was only one phase 3 clinical trial, which compared a stem cell transplantation group, a rehabilitation group, and a blank control group [43]. The route of administration was injection the injured area, intrathecal injection, and intravenous infusion. Three studies performed stem cell therapy together with other treatments, such as decompression of the spinal lesion; physiotherapy involving mat activities, strengthening exercises, self-range of motion, ambulation training for paraplegic patients, and cardiopulmonary training; and rehabilitation therapy [39,41,43].

The baseline severity of SCI was classified according to the American Spinal Injury Association (ASIA) impairment score. After stem cell treatment, sensory and motor function was evaluated with the ASIA impairment score, the Association Impairment Scale score, and somatosensory evoked potentials. Some studies used computed tomography and magnetic resonance imaging of the spinal cord to assess structural changes after stem cell treatment. The 6 studies that reported results showed improvements in sensory and motor function, regardless of the types of stem cells and administration route. A combination of stem cell therapy with physiotherapy and rehabilitation therapy showed remarkable improvements in motor function compared with the patients treated with physiotherapy and rehabilitation therapy only. In addition, no severe adverse events were observed in any studies, and only mild and transient adverse events such as headache, low-level pain, and nonspecific tingling sensations were reported.

PRECLINICAL STEM CELL THERAPY FOR THE TREATMENT OF NEUROGENIC BLADDER AFTER SPINAL CORD INJURY

NB is a commonly observed functional impairment after SCI, and several animal studies have evaluated the effects of stem cell therapy on bladder function. Previous studies used various SCI animal models to represent NB in SCI patients, and SCI was induced by contusion, transection, and needle-stick injury of the spinal cord [44-50]. Five different sources were used: BM-MSCs, human UC-MSCs, neuronal stem cells, human MSCs, and oral mucosa stem cells. Most of the studies administered stem cells through direct injection to the injured area between 3 days and 13 weeks after the injury. Bladder function was evaluated by performing a urodynamic study (UDS) after stem cell therapy. Compared with the SCI group without treatment, the stem cell therapy group showed decreased voiding pressure and non-voiding contraction and increased bladder compliance and bladder capacity. In addition to UDS, some previous studies simultaneously evaluated sensory and motor function. Functional changes after stem cell therapy varied from minimal to a significant improvement.

CLINICAL TRIALS OF STEM CELL THERAPY FOR NEUROGENIC BLADDER AFTER SPINAL CORD INJURY

There were 10 clinical trials of stem cell therapy for NB after SCI that included evaluations of bladder function. Among them, 5 studies were completed, and 5 studies were ongoing (Table 2). All of them except 1 study (phase 3) [43] were phase 1 or 2 clinical trials, and they used stem cells such as autologous BM-MSCs, UC-MSCs, Wharton's jelly MSCs, and human-spinal cord-derived neural stem cells. The administration route in most of these studies was intrathecal injection. In 1 study (NCT01909154; see Table 1), a second injection was performed 3 months after the first injection. Bladder function was evaluated with UDS in the completed clinical trials except for 1 study (NCT02570932). Increased maximum cytometric capacity, improved compliance, and decreased detrusor pressure were noted, with results comparable to those of preclinical studies. However, these improvements of UDS did not reduce urinary incontinence or eliminate the need for clean intermittent catheterization (CIC). Five ongoing clinical trials are planning to evaluate bladder function with UDS, measurements of postvoid

Table 2. Clinical trials including evaluations of neurogenic bladder (http://clinicaltrials.gov/)

Identifier	Clinical trial phase	Type of SCI	No. of patients	Age (yr), range	Cell type	Delivery method	Efficacy	UDS	Safety
Completed trials									
NCT02152657	Phase 1	Chronic SCI (ASIA grade A)	5	18–65	Autologous BM-MSCs	Percutaneous administration	NR	NR	NR
NCT01325103 [39]	Phase 1	Thoracic or lumbar traumatic SCI (ASIA grade A)	14	18–65	Autologous BM-MSCs	Intralesional injection after laminectomy and decompression of the spinal lesion area	Variably enhanced sensitivity below the injury area was observed. 9 patients: improvement of lower limb motor function, 7 patients: improvement of AIS, 3 patients: improvement of neuropathic pain	Increased maximum cystometric capacity without significance, significant improvement of compliance, improvement of bladder sensation. Urinary incontinence was not improved. CIC was needed after treatment	14 patients: discharge within 48 hours after surgery, 1: cerebrospinal leak related to surgery, No severe adverse events
NCT01909154	Phase 1	Chronic paraplegia (ASIA grade A)	9	18–50	Autologous BM-MSCs	Intrathecal injection (second injection at 3 months after the first injection)	Sensory recovery, improvement of chronic pain, presence of SSEPs	Increased bladder compliance, decreased detrusor pressure	No severe adverse events, nausea, urinary tract infection, back pain, thoracic pain, muscle contracture, myalgia, headache
NCT02570932	Phase 2	Chronic SCI	10	18–70	Autologous BM-MSCs	Intrathecal injection	NR	NR[a)]	NR
NCT01393977 [43]	Phase 3	Thoracolumbar SCI	34	20–50	UC-MSCs transplantation group, rehabilitation therapy group, control group	Intrathecal injection	Seven of 10 patients treated with UC-MSCs showed significant improvement of motor function.	Significantly increased maximum bladder capacity, significantly decreased detrusor pressure, increased maximum flow rate without significance	Radiating neuralgia after UC-MSC transplantation; improvement within 24 hours
Ongoing trials									
NCT03521336	Phase 2	Subacute SCI	84	18–65	BM-MSCs	Intrathecal injection	NR	NR	NR
NCT03521323	Phase 2	Early-stage of chronic SCI	66	≥18	BM-MSCs	Intrathecal injection	NR	NR	NR
NCT03003364	Phase 1/2	Chronic SCI	10	18–65	WJ-MSC	Intrathecal injection	NR	NR	NR
NCT02687672	Phase 2	Chronic complete SCI	50	5–50	Autologous BM-MSCs	NR	NR	NR	NR
NCT01772810	Phase 1	Chronic SCI	8	18–65	Human-spinal cord-derived neural stem cell	NR	NR	NR	NR

SCI, spinal cord injury; UDS, urodynamic study; ASIA, American Spinal Injury Association; BM-MSCs, bone marrow stem cells; AIS, Association Impairment Scale; SSEP, somatosensory evoked potential; ADSCs, adipose-derived mesenchymal stem cells; BM-MSCs, umbilical cord mesenchymal stem cells; CIC, clean intermittent catheterization; WJ-MSCs, Wharton's jelly mesenchymal stem cells; NR, not reported.

[a)]Bladder function was evaluated with the Neurorestoratology-Spinal Cord Injury Functional Rating Scale.

residual urine volume, and data obtained via questionnaires.

WHAT IS NECESSARY FOR CLINICAL APPLICATIONS?

Increasingly many preclinical and clinical studies have investigated the effects of stem cell therapy on NB related to SCI, and several positive results have been reported in previous clinical trials. However, many questions remain about the effects and safety of stem cell therapy. Most of the previous clinical trials were not randomized trials, did not have a control group, and included a small number of patients. Moreover, the dose, route of administration, and timing were different in each of the studies. Furthermore, no studies demonstrated functional recovery of voiding; as mentioned above, patients still had persistent urinary incontinence and a continuing need for CIC. Furthermore, no study showed improvements in sensory and motor function after stem cell therapy. Therefore, further studies are necessary to demonstrate clear evidence regarding stem cell therapy and the appropriate direction for standardization of therapeutic methods. Moreover, the Tissue Engineering & Regenerative Medicine International Society (TERMIS) suggested 5 significant drivers for the translation of regenerative medicine, including stem cell therapy, to real clinical practice [51]. The major drivers pointed out by TERMIS are: fully validated manufacturing capability for stem cells, reimbursement for NB related to SCI, regulation of the design and development of stem cells that will show consistent effect and safety, collaboration among various researchers and economic actors, and clinical development plans to reduce the risk of failure.

CONCLUSIONS

Stem cell therapy is a promising therapeutic option for NB related to SCI, and many preclinical and clinical studies have been conducted to demonstrate the efficacy and safety of stem cell therapy. Several clinical trials have demonstrated improvements in bladder function. However, clear evidence is lacking because most of the extant clinical trials were not high-quality, and therapeutic methods varied among the studies. Therefore, there is a pressing need for further studies to demonstrate evidence of the therapeutic potential of stem cell therapy and to enable the translation of stem cell therapy to real-world practice.

AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: *SJK*
- Formal Analysis: *YSC*
- Investigation: *SJK, YSC*
- Methodology: *SJK, YSC, JMP*
- Project Administration: *KHK*
- Writing – Original Draft: *SJK*
- Writing – Review & Editing: *KHK, YGN*

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