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Review Article

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Induced Neural Stem Cell Transplantation in Spinal Cord Injury: Present Status and Next Steps

Jae-Woo Jung [1], **Je Hoon Jeong** [2], **Myeong Jin Ko** [3], **Byung-Jou Lee** [4], **Woo-Keun Kwon** [5], **Sang Ryong Jeon** [6], **and Subum Lee** [1]

[1]Department of Neurosurgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
[2]Department of Neurosurgery, Soonchunhyang University Bucheon Hospital, Bucheon, Korea
[3]Department of Neurosurgery, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea
[4]Department of Neurosurgery, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
[5]Department of Neurosurgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[6]Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Address for correspondence:
Subum Lee
Department of Neurosurgery, Korea University Anam Hospital, Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea.
Email: lee_s@korea.ac.kr

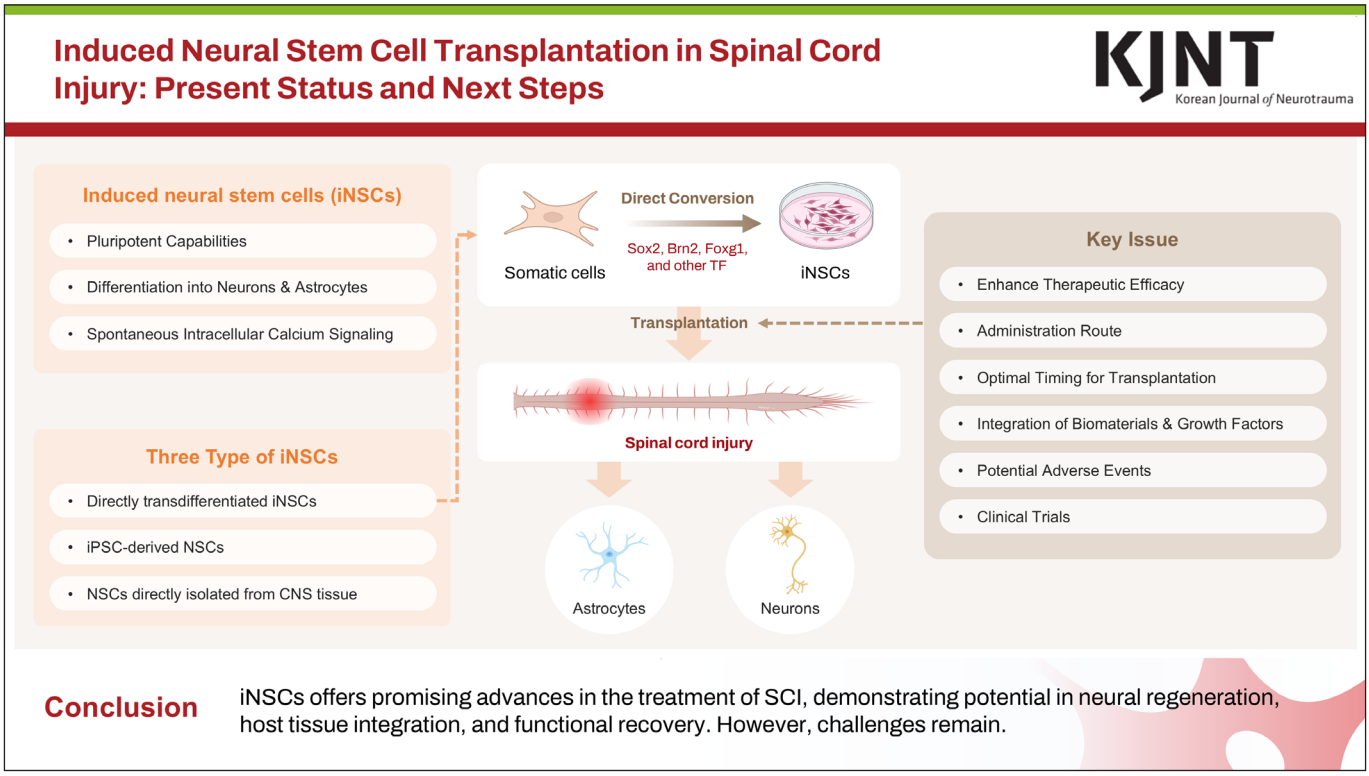
ORCID iDs
Jae-Woo Jung
https://orcid.org/0009-0004-3711-8405
Je Hoon Jeong
https://orcid.org/0000-0002-4656-0113
Myeong Jin Ko
https://orcid.org/0000-0002-1850-7753
Byung-Jou Lee
https://orcid.org/0000-0002-4030-3618

ABSTRACT

Spinal cord injury (SCI) remains a significant clinical challenge, with no fully effective treatment available despite advancements in various therapeutic approaches. This review examines the emerging role of induced neural stem cells (iNSCs) as promising candidates for SCI treatment, highlighting their potential for direct neural regeneration and integration with host tissue. We explore the biology of iNSCs, their mechanisms of action, and their interactions with host tissue, including modulating inflammatory responses, promoting axonal growth, and reconstructing neural circuits. Additionally, the importance of administration route, optimal timing for transplantation, and potential adverse events are discussed to address key challenges in translating these therapies to clinical applications. The review also emphasizes recent innovations, such as combining iNSC transplantation with rehabilitative training and the integration of biomaterials and growth factors to enhance therapeutic efficacy. Although preclinical studies have demonstrated positive outcomes, larger, controlled trials and standardized protocols are essential for validating the safety and effectiveness of iNSC-based therapies for SCI patients.

Keywords: Spinal cord injury; Neural stem cells; Cell- and tissue-based therapy; Regenerative medicine; Transplantation

GRAPHICAL ABSTRACT



Woo-Keun Kwon
https://orcid.org/0000-0003-0432-8620
Sang Ryong Jeon
https://orcid.org/0000-0002-8340-7978
Subum Lee
https://orcid.org/0000-0003-4732-8137

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Informed Consent
This study does not require informed consent.

Ethics Approval
This study does not require ethics approval.

INTRODUCTION

Currently, there is no fully effective treatment for spinal cord injury (SCI), despite various therapeutic strategies being investigated.[7,29] Globally, there were 0.9 million incident cases and 20.6 million prevalent cases of SCI in 2019, representing a significant healthcare challenge worldwide.[13] The economic burden of SCI is substantial, encompassing both direct medical costs and indirect losses due to decreased productivity and quality of life.[30,58]

Treatment approaches could be categorized into several main areas: cellular therapies, rehabilitation strategies, and biomaterial applications.[4,22,40,46,47] Among cellular therapies, mesenchymal stem cells (MSCs) have been the most widely studied and clinically tested cell type, known for their anti-inflammatory properties and ability to promote vascular regeneration.[63] However, their limited capacity to differentiate into neural cells remains a significant drawback.[22]

Induced neural stem cells (iNSCs) have recently emerged as promising candidates for SCI treatment, offering advantages such as direct neural regeneration potential and superior integration with host spinal cord tissue.[24] Despite these benefits, concerns remain regarding their tumorigenic potential, low survival rates, and possible immune rejection responses.[56] Indeed, stem cell therapy faces several challenges, including the potential risk of tumorigenesis, poor cell survival in the hostile environment of the injured spinal cord, and limited integration with host tissue.

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Recent advances in stem cell biology have opened new avenues for regenerative medicine, particularly through the development of iNSCs. Preclinical studies have demonstrated encouraging results, particularly when iNSC transplantation is combined with rehabilitative training. These studies have shown enhanced survival rates and neuronal differentiation of transplanted cells, along with improved motor function recovery.[56]

The translation of these promising preclinical findings into clinical applications represents the next crucial step in developing effective treatments for SCI patients. Current research focuses on optimizing treatment protocols, improving cell survival rates, and enhancing functional outcomes through combination therapies.[22]

BIOLOGY OF NEURAL STEM CELLS

The transplantation of neural stem cells (NSCs) holds substantial therapeutic potential for treating various neurodevelopmental, neurodegenerative, and neurotraumatic conditions by aiding in restoring and replacing damaged neuronal networks.[62] An essential initial focus is to explore the acquisition of NSCs, considering both the sources of these cells and the dosage required for effective transplantation. Presently, there are three primary sources for obtaining NSCs: direct extraction from primary central nervous system (CNS) tissue (from either fetal or adult brain sources), differentiation of pluripotent stem cells, and transdifferentiation from somatic cells.[49]

iNSCs represent a significant advancement in cellular therapy through their direct reprogramming from somatic cells. This process, achieved by introducing specific transcription factors such as Sox2, Brn2, and Foxg1, bypasses the pluripotent state, offering advantages over traditional induced pluripotent stem cells (iPSCs).[50,56] The direct conversion approach reduces the risk of tumorigenicity while maintaining the desired NSC properties (**FIGURE 1**).

Functionally, iNSCs demonstrate remarkable pluripotent capabilities, including differentiation into neurons and astrocytes, and exhibit spontaneous intracellular calcium signaling. These cells can develop into functionally mature neurons, with their differentiation process critically regulated by the Wnt/β-catenin pathway and trophoblast glycoprotein levels.[28,35] This controlled differentiation process is essential for successful therapeutic applications.

Upon successful transplantation and differentiation, these cells demonstrate remarkable integration capabilities with host neural networks. The transplanted cells differentiate into both neurons and glia, effectively filling lesion cavities in injured areas.[36,60] Most significantly, they establish functional synapses with host tissue and demonstrate the ability to create new neural circuits within existing networks. This integration is facilitated by the capacity of transplanted cells to extend axons both cephalad and caudally from the injury site, reaching distances up to approximately 6 cm into supraspinal structures.[36,60] Such extensive axonal growth and integration capabilities are crucial for establishing functional neural connections and promoting recovery after SCI.

The discovery of iPSCs has been a groundbreaking advancement in regenerative medicine and biological research. The ability to convert adult somatic cells, such as blood cells or skin fibroblasts, into NSCs via iPSCs has spurred extensive research in the field. Encouraging

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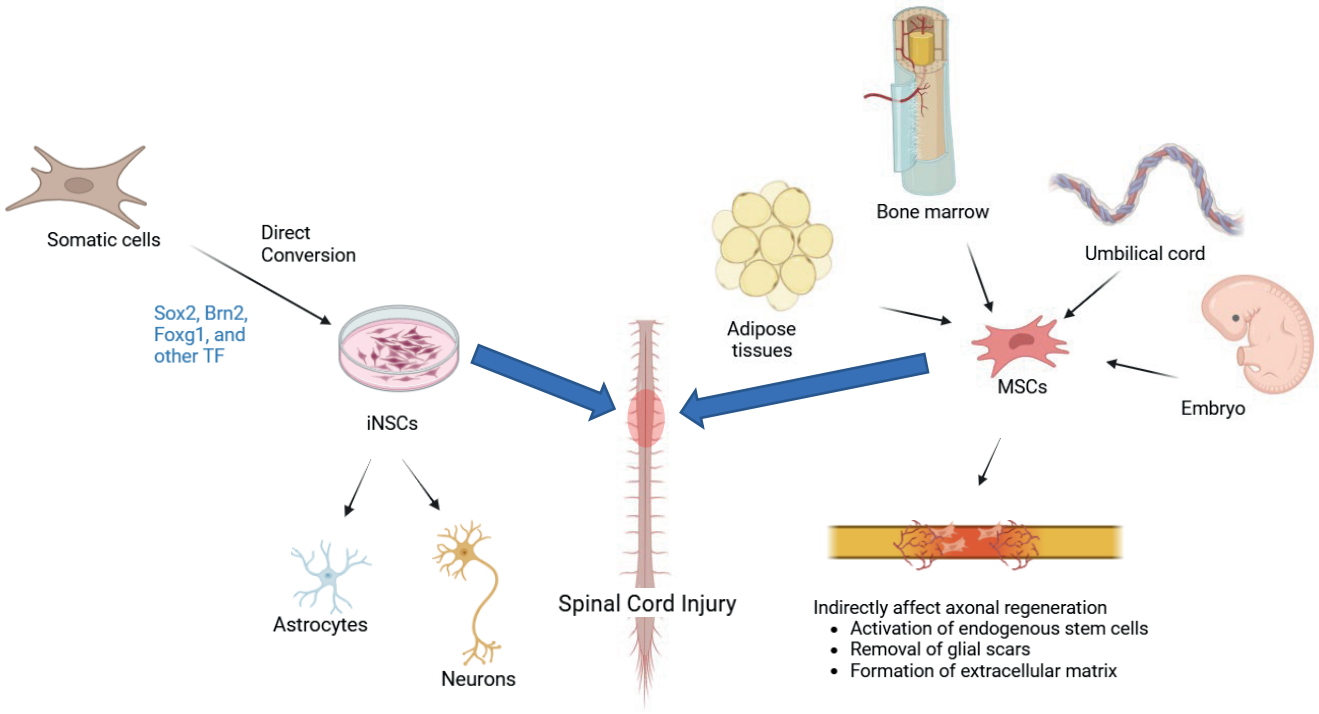

FIGURE 1. Comparison of iNSCs (left) and MSCs (right): iNSCs, reprogrammed from somatic cells, focus on neuronal regeneration and neurotrophic support, while MSCs, derived from bone marrow, adipose, or umbilical cord, provide anti-inflammatory, immunomodulatory effects, and extracellular matrix remodeling for spinal cord injury repair.
iNSC: induced neural stem cell, MSC: mesenchymal stem cell.

outcomes have been documented following the transplantation of iPSC-derived NSCs into animal models of SCI, where these cells have demonstrated improved survival, tissue preservation, and differentiation into neurons. Furthermore, functional recovery has been noted, supported by axon remyelination and increased levels of neurotrophic factors within the spinal cord.[2,51]

CLASSIFICATION OF iNSC TYPES

iNSCs can be categorized into 3 major types based on their derivation sources and generation methods. The first category includes directly transdifferentiated iNSCs, which are generated from somatic cells such as fibroblasts or peripheral blood mononuclear cells through the forced expression of specific transcription factors.[14,43] These cells are advantageous due to their faster generation time and reduced risk of tumor formation compared to other methods, making them a promising option for clinical applications.[14] The second category consists of iPSC-derived NSCs, which are created through an intermediate pluripotent state using OSKM factors (Oct3/4, Sox2, Klf4, and c-Myc). This approach produces high cell yields but raises concerns regarding tumorigenicity, as residual undifferentiated cells may remain after differentiation.[20] The third category includes NSCs directly isolated from CNS tissue. These cells serve as a natural source of neural progenitors but face practical limitations, such as restricted accessibility and low scalability, which hinder their broader application.[43] Each type of iNSC exhibits distinct clinical potential. Transdifferentiated iNSCs are particularly promising for treating SCIs due to their efficient differentiation into neuronal lineages

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and their ability to form functional synapses with host neurons.[20] These cells also exhibit immunomodulatory properties and support endogenous tissue regeneration without inducing tumor formation, underscoring their value for therapeutic use.[14]

HOST TISSUE RESPONSE

Host tissue response to transplanted iNSCs after SCI demonstrates complex and multifaceted processes. The primary responses occurring in the damaged spinal cord tissue include: in the initial phase, detrimental cellular processes occur at the injury site, such as axonal degeneration, neuronal cell loss, neuroinflammation, reactive gliosis, and scar formation.[9] Transplanted iNSCs elicit specific responses in host tissue that facilitate recovery. They modulate glial scar formation by reducing the accumulation of scar matrix, which promotes long-distance axonal growth and neural connectivity.[34]

Additionally, iNSCs regulate inflammatory responses in both the acute and chronic phases by altering the expression of inflammatory mediators like tumor necrosis factor, thereby influencing the activation, mobilization, and polarization of microglia and infiltrating immune cells.[37] These cells also contribute to the reconstruction of neural circuits within the damaged spinal cord, restoring connectivity with supraspinal pathways.[37]

Collectively, these host tissue responses lead to significant improvements in motor and sensory function.[34] Notably, human neural stem cells (hNSCs) with reduced *SOX9* gene expression demonstrate enhanced integration with host tissues and an increased tendency to differentiate into motor neurons, further supporting functional recovery.[34]

ANIMAL MODELS AND TRANSPLANTATION TIMING

Animal studies investigating iNSC transplantation in SCI have demonstrated promising therapeutic outcomes across various injury phases. Significant functional improvements were observed in all treatment periods, with transplantation in the subacute phase (3–14 days post-injury) emerging as the optimal window for treatment.[54] Based on systematic reviews and meta-analyses, higher doses ($\geq 1\times10^6$ cells) yielded superior results, particularly when delivered through intra-lesional transplantation.[55]

Histopathological analyses confirmed successful cell engraftment, with transplanted cells migrating to both rostral and caudal regions of the lesion site and showing preferential differentiation into oligodendrocytes, resulting in reduced astrogliosis, enhanced tissue preservation, and promoted remyelination of preserved tissue.[1]

The timing of stem cell transplantation following SCI is a critical factor in treatment outcomes. Administering cells at an acute stage may be more effective in repairing damaged neural circuits before the glial scar barrier forms. However, the substantial number of chronic patients underscores the need to develop innovative strategies to enhance the effects of cell transplantation during the chronic phase. Additional preclinical studies are required to better determine the optimal timing for NSC transplantation. As is well known, SCI is a 2-phase process with complex cellular and molecular responses that evolve over time, making it challenging to pinpoint the best treatment window. Among the stages of

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injury—acute (within 24 hours post-injury), subacute (3–14 days post-injury), and chronic (after 14 days post-injury)—the subacute period is considered the most effective window for performing transplantation surgery.[6,56] Notably, experimental studies involving intrathecal transplantation of MSCs in adult rats have identified days 7–9 post-injury as the optimal timing for transplantation.[8] Many researchers have conducted numerous studies on stem cell transplantation therapy for subacute SCI and have shown the efficacy of cell transplantation therapy.[25,45] Clinical trials in human patients have also been initiated based on the results of preclinical studies.[59]

While these results are encouraging, current limitations include relatively fewer studies on chronic phase treatment and the need for research in more severe injury models, with recent reviews emphasizing the importance of standardizing experimental protocols and improving the quality of animal studies to facilitate better clinical translation.[3] The microenvironment of the chronically injured spinal cord is very different from that in the subacute phase, and the spinal cord is extremely difficult to regenerate owing to various factors that inhibit axon extension and cavity formation. In particular, scarring is a significant problem in cell transplantation therapy for chronic SCI because it prevents the engraftment of transplanted cells.[56]

ROUTE OF ADMINISTRATION (INTRATHECAL, INTRALESIONAL, INTRAVENOUS INJECTION)

The administration route is a critical factor to consider in cell transplantation. In the context of SCI, three primary injection methods have been explored: intrathecal, intralesional (i.e., intraspinal) and intravenous. The intrathecal injection method delivers stem cells into the subarachnoid space, with several notable characteristics. This approach is minimally invasive, performed via lumbar puncture, and allows for wide distribution as cerebrospinal fluid circulation facilitates the spread of stem cells to a broad area, including the injury site. It also has a high potential for repeated administration and is relatively safe.

In contrast, intralesional transplantation involves directly implanting stem cells into the injured spinal cord area. Key features of this approach include precise targeting, as stem cells can be directly delivered to the damaged site, and high engraftment rates due to the direct implantation, which supports more remarkable cell survival. However, it requires surgical access, making it a more invasive procedure.

Intralesional transplantation demonstrates a higher cell engraftment rate when considering cell survival and distribution. Experimental studies have shown that an average of 25.6–26.7 cells per high-power field survive with intralesional transplantation, compared to an average of only 20.6 cells for intrathecal injection.[26] Regarding timing and frequency, studies indicate that a shorter time to treatment initiation post-injury and more frequent stem cell injections increase the likelihood of functional recovery.[61] Both methods share therapeutic mechanisms, including neuron repair or replacement, neurotrophic factor secretion, and suppression of localized inflammatory responses,[17] as previously discussed (**TABLE 1**).[15,26,61]

In selecting a clinical treatment approach, factors such as the acute or chronic nature of the injury, the number of cells to be delivered (ranging from tens of thousands to millions), and the potential use of immune suppressants should be considered.[15] Given these characteristics, intralesional transplantation is preferred when precise targeting and high

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TABLE 1. Route of administration - intrathecal and intralesional

	Intrathecal injection	Intralesional transplantation
Invasiveness[15]	Minimally invasive through lumbar puncture	Highly invasive requiring surgical exposure of injury site
Technical difficulty[61]	Relatively easy to perform via subarachnoid space	Technically complex, requires precise surgical targeting
Cell distribution[26]	Widespread distribution through cerebrospinal fluid circulation	Localized distribution directly at injury site
Cell survival rate[26]	Lower engraftment rate	Higher engraftment rate
Repeat administration[61]	Easy to repeat multiple injections	Limited by surgical risks and tissue scarring
Risk of complications[15]	Lower risk due to minimal invasion	Higher risk due to surgical intervention

cell survival are required, whereas intrathecal injection is more suitable when repeated administration is necessary or when a less invasive approach is desired.

Meanwhile, there are studies reporting positive outcomes with intravenous administration as well. Nishimura et al.[44] observed that animals receiving hNSCs via intravenous injection demonstrated behavioral improvements, electrophysiological recovery, reduced glial scar formation, and preservation of nerve fibers. These findings suggest that the cells can survive, proliferate, and migrate to the lesion site. Additionally, Osaka et al.[48] also support intravenous delivery of cells as a minimally invasive approach with significant therapeutic potential.

Further research is needed to determine the optimal route of administration. Minimally invasive methods reduce surgical risks for patients, but they may compromise some therapeutic efficacy. It is essential to thoroughly investigate these factors in preclinical studies to find the best balance between safety and effectiveness.

ADVERSE EVENTS

The most common adverse events following cell therapy for SCI are primarily associated with neurological symptoms. These include transient back pain and meningism, reported in approximately 90% of cases, as well as spinal cord malacia, observed in 80% of patients. Peripheral neurological symptoms, such as neuropathic pain, increased muscle tone, spasticity, and rigidity, are also frequently reported, along with incision site pain, allodynia, and hyperalgesia.[19]

Local complications at the injection site represent another significant category of adverse events. The most prevalent of these is cerebrospinal fluid leakage, followed by wound infections and delayed healing. Systemic reactions have also been documented, including fever (14.1%), headache (4.2%), transient muscle tone increase (1.6%), and dizziness (1.3%). Additionally, skin manifestations, such as facial flushing or rash, have been reported in some cases.[21]

A key concern is the risk of tumorigenicity, particularly given the stem cell nature of iNSCs. While certain studies have reported no tumor formation,[27,53] others have documented tumorigenic risks, particularly linked to pluripotent-derived NSCs.[41,52] As research progresses, more evidence has emerged regarding the tumorigenic potential of iPSC-derived NSCs, which must be carefully managed to ensure high clinical standards in applying these therapies. The pathological mechanisms underlying this risk involve complex interactions between immune and neural cell responses, with dynamic changes occurring primarily at three days post-injury and a second wave of microglial activation around day 14.[21]

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Tumorigenicity mainly presents in two forms: teratoma formation and true tumor development.[5,23] However, the precise mechanisms driving each are not yet fully understood. Some studies suggest that factors used in the reprogramming process and any residual undifferentiated cells may lead to epigenetic changes that increase the tumorigenic potential of iPSC-derived NSCs.[12,38] Teratoma formation is primarily linked to the "epigenetic memory" retained within the cells and the lack of sufficient purification in the cell samples intended for transplantation.[12] Strategies to address these risks include increasing the number of cell passages to reduce "epigenetic memory," developing more effective purification systems, reprogramming iPSCs to avoid teratoma-inducing pathways, and even transplanting cells at a more differentiated state to mitigate these risks. Notably, meta-analyses have indicated that the overall prevalence of adverse events in cell therapy is approximately 19%,[11] with NSCs being among the cell types most associated with these effects.

CLINICAL TRIALS

A comprehensive review of stem cell-based therapies for SCI has provided significant insights into their therapeutic potential. Recent systematic analysis of 66 clinical studies, involving 1,086 patients, revealed that cervical injuries were most prevalent (42.2%), with bone marrow-derived stem cells being the predominant cell type used (71.1% of studies).[1]

Clinical outcomes from these trials have shown varying degrees of success. A systematic review of 53 studies (including 21 clinical trials) demonstrated consistent improvements in American Spinal Injury Association Impairment Scale (AIS) grades and enhanced sensory scores, though motor function improvements remained relatively modest.[42] The majority of these studies were phase I/II trials, employing either direct surgical implantation or injection into the spinal cord or submeningeal spaces. Safety profiles from both general stem cell trials and iNSC-specific studies have been generally favorable, with most adverse events being mild and transient.[18,42]

In recent years, iPSC-derived NSC therapy has emerged as a promising approach.[56] Preclinical studies have demonstrated several key mechanisms of therapeutic efficacy, including enhanced survival rates and successful neuronal differentiation of transplanted human-induced pluripotent stem cell-derived neural stem/progenitor cells (hiPSC-NS/PCs). The first-in-human clinical trial using hiPSC-NS/PCs for subacute SCI has been initiated, marking a significant milestone in the field.[59] However, clinical trials investigating NSC treatment for patients with SCI have been limited in number.[31] It is encouraging, however, that several studies have reported both procedural safety and some degree of functional recovery following NSC transplantation in SCI patients.[16,32,57] Nevertheless, due to the small sample sizes and the fact that most trials included only patients in the subacute (1 week to 6 months post-injury) and chronic (over 6 months post-injury) phases, determining the therapeutic efficacy of NSCs, particularly for acute phase SCI, remains challenging (**TABLE 2**).[10,16,31-33,39,57]

FUTURE PERSPECTIVE

Current challenges in the field include the need for standardized protocols, optimization of delivery methods, and the establishment of larger controlled trials. The timing of intervention appears crucial, with different efficacy levels observed between subacute and

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TABLE 2. Summary of clinical studies using iNSCs for human SCI treatment in the last decade

Study	Year	Key findings	SCI stage targeted	Administration route	Primary outcome
Shin et al.[57]	2015	· 5/19 patients showed motor and sensory improvements. Transplanted cells were well tolerated without serious adverse events. Preliminary data showed limited but measurable neurological recovery.	Cervical SCI (AIS A and B); Treatment initiated 16–213 days post-injury	Direct intralesional transplantation 1.0 mL, 1.0×10^5 cells per μL center, 5 mm rostral & caudal	Safe and feasible with modest neurological recovery.
Levi et al.[32]	2019	· HuCNS-SC transplantation demonstrated safety across multiple centers. Trends in motor score improvements were noted, although not statistically significant.	Chronic cervical SCI (C5–C7, AIS A and B); Treatment initiated 4–24 months post-injury months	Perilesional intramedullary injections Dose: from 15,000,000 to 40,000,000 cells	Safe and tolerable with early indications of efficacy.
Curtis et al.[10]	2018	· 2/4 patients demonstrated motor score improvements, achieving 2 levels of recovery. No major adverse events were reported over 1 year.	Chronic thoracic SCI (T2–T12, AIS A); Treatment initiated >1 year and <2 years post-injury	Six intraspinal injections (2×10^5 cells/injection) The injections were placed bilaterally into the remaining tissue lateral to the injury site and within the medial white matter-appearing tracts of approximately one segment below the injury site	Safe and effective in demonstrating early functional recovery.
Levi et al.[33]	2018	· No evidence of tumor formation or adverse events directly related to cells. Mild functional improvements were seen in some participants over 12 months.	16 to 104 weeks post injury	Manual (free-hand) intramedullary transplantation Dose: >20, <40 million cells	Surgical safety and tolerability with modest benefits.
Ghobrial et al.[16]	2017	· All patients tolerated the procedure. Modest improvements in sensory and motor functions were observed. No new lesions or syrinx formation noted.	At least 4 months after injury	Rostral and caudal to the lesion site with a 2-hand technique, intramedullary injections Dose: 40 million cells	Safe with mild functional recovery.
Martin et al.[39]	2024	· Safe and feasible for chronic SCI treatment. · 2/4 patients showed durable neurological improvements, including increased motor and sensory scores. · Tolerability of the procedure was confirmed with no major adverse events.	Chronic thoracic SCI (T2–T12, AIS A); Treatment initiated >1 & <2 years post-injury	Intramedullary, a dose of 2×10^5 cells per injection site bilaterally into the remaining tissue lateral to the injury site	Safety and feasibility assessment of NSI-566 transplantation.

iNSC: induced neural stem cell, SCI: spinal cord injury, AIS: American Spinal Injury Association Impairment Scale.

chronic phases. Recent innovations have focused on combination approaches, particularly the integration of hiPSC-NS/PC transplantation with rehabilitative training, which has shown enhanced therapeutic outcomes compared to single-treatment approaches.

The field continues to evolve with particular emphasis on developing comprehensive treatment strategies that combine cellular therapy with rehabilitation protocols and bioengineering approaches. Future directions point toward the need for more rigorous trial designs and more extended follow-up periods to assess long-term safety and efficacy better.

CONCLUSION

In summary, the application of iNSCs offers promising advances in the treatment of SCI, demonstrating potential in neural regeneration, host tissue integration, and functional recovery. However, challenges remain, including the need for standardized protocols, optimization of cell administration routes, and larger clinical trials to validate findings. Recent advancements in combination therapies, such as the integration of rehabilitative training and biomaterials, show potential to enhance iNSC efficacy. Continued research is necessary to refine these strategies, address long-term safety concerns, and bring effective iNSC-based therapies closer to clinical reality for SCI patients.

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