LONG-TERM EVALUATION OF THE SAFETY AND EFFECTIVENESS OF NEURAL STEM CELL TRANSPLANTATION FOR CHRONIC THORACIC SPINAL CORD INJURY

Harmin[1*], Hanisa Aulia Maharani[2]

[1]Medicine, Faculty of Medicine, Adiwangsa Jambi University

[2]Medicine, Faculty of Medicine, Adiwangsa Jambi University

[*] Corresponding author : harminmedadiwangsa@gmail.com

ABSTRACT

Spinal cord injury (SCI) is a debilitating neurological condition that leads to partial or complete loss of motor and sensory function, depending on the injury's severity and location. Conventional therapies focus on surgical stabilization, prevention of secondary damage, and rehabilitation. However, these approaches often fall short in restoring long-term functionality. In recent years, cell-based therapies have emerged as promising alternatives, particularly those involving neural stem cells (NSCs). This literature review explores the long-term safety and effectiveness of NSC transplantation for chronic thoracic SCI, based on studies published between 2010 and 2025. Research shows that fetal-derived NSCs, such as HuCNS-SC, demonstrate a high safety profile and low risk of tumor formation due to their committed neural lineage. Clinical trials report early signs of motor improvement and reduced spasticity in chronic SCI patients following transplantation. Additionally, mesenchymal stem cells (MSCs) have shown the ability to migrate to injury sites and exert therapeutic effects, though these benefits tend to be short-lived. The post-injury inflammatory microenvironment poses a significant barrier to the success of NSC therapies by impairing stem cell differentiation and survival. Therefore, immunosuppressive regimens are often employed to enhance NSC efficacy by creating a more supportive environment. Overall, while both NSCs and MSCs offer promising avenues for SCI treatment, long-term recovery likely requires multimodal approaches that address both neural regeneration and immune modulation. Continued research is essential to optimize these therapies and translate them into effective clinical treatments for patients with chronic SCI.

Keywords : Spinal cord injury, neural stem cells, mesenchymal stem cells, neural lineage

INTRODUCTION

Spinal cord injury (SCI) is a serious neurological condition that significantly impacts the quality of life of millions of individuals worldwide. This injury leads to substantial neurological impairments, ranging from loss of sensory function to paralysis, depending on the severity and location of the damage. To date, the management of SCI has focused on three main aspects: initial stabilization of the injury, prevention of secondary damage, and rehabilitation efforts aimed at restoring bodily functions as optimally as possible. Common conventional therapies include surgical interventions to repair damaged spinal structures and neurological rehabilitation programs to retrain the patient's motor and sensory abilities

(Srikandarajah et al., 2023; Baroudi et al., 2024).

The most common symptom of spinal cord injury (SCI) is sensorimotor deficit, either partial or complete, which arises from the disruption of sensory and motor pathways that connect the brain to the body through the spinal cord. These pathways play a crucial role in enabling the brain to receive sensory information from the environment and send motor commands to the body's muscles. Therefore, when damage occurs to the spinal cord, communication between the brain and the parts of the body below the injury site is impaired, resulting in loss of sensory and motor functions (Moreno-López & Hollis, 2021; Li et al., 2024; Iversen et al., 2024).

The distribution of SCI along the spinal cord is not uniform. The majority of injuries are reported in the cervical segment, followed by the thoracic and then the lumbosacral segments. The location of the injury carries significant clinical implications, as SCI typically affects all body structures innervated by nerves below the level of the injury. As a result, the higher the injury—such as in the cervical region—the more extensive the area of the body that will be affected, increasing the level of disability and the complexity of treatment (Chiu et al., 2024).

In addition to motor and sensory impairments, SCI can also lead to a range of systemic complications that contribute to reduced quality of life. These complications include bladder control issues, sexual dysfunction, persistent chronic pain, and mood disorders such as depression and anxiety. The combination of neurological deficits and psychosocial challenges makes SCI a multidimensional condition that requires a comprehensive and ongoing therapeutic approach (Denys et al., 2021; Mahler et al., 2025).

Over the past decade, advances in the biomedical field have opened new opportunities through innovative therapeutic approaches such as neuromodulation and cell-based therapies. Neuromodulation involves manipulating nervous system activity through electrical stimulation or other techniques to modulate impaired neural functions. Meanwhile, cell-based therapies, particularly those involving the use of stem cells, offer promising regenerative potential to repair nerve tissues damaged by SCI. Among the various types of stem cells being studied, fetal-derived neural stem cells (NSCs) stand out due to their high safety profile. This is attributed to their predetermined differentiation toward neural lineages and their low propensity to form teratomas, a type of tumor commonly associated with the use of other stem cells. With these characteristics, NSCs are considered a promising candidate in the development of regenerative therapies for SCI in the future (Guo et al., 2022; Gelenitis et al., 2024; Li et al., 2024; Martin et al., 2024).

MATERIALS AND METHODS

This literature review was conducted to evaluate the long-term safety and effectiveness of neural stem cell (NSC) transplantation for chronic thoracic spinal cord injury (SCI). A comprehensive and structured search of scientific publications was performed across multiple databases, including PubMed, Google Scholar, and ScienceDirect, focusing on studies published between January 2010 and April 2025.

The keywords used in the search included combinations of the following terms: "neural stem cell transplantation," "chronic spinal cord injury," "thoracic SCI," "long-term outcomes," "safety," and "effectiveness." Boolean operators such as AND and OR were used to refine and narrow down the search results. Only articles written in English and involving in vivo human or animal studies were considered.

The inclusion criteria for this review were:
(1) original research articles evaluating the transplantation of neural stem cells in chronic thoracic spinal cord injury models or patients
(2) studies with follow-up duration of at least 6 months
(3) studies reporting specific outcomes related to functional recovery, adverse effects, histological findings, or electrophysiological assessments.

Exclusion criteria included:
(1) reviews, editorials, and case reports with insufficient data
(2) studies focusing exclusively on acute or subacute spinal cord injuries
(3) articles without available full text or lacking relevant outcome measures.

All relevant articles were screened based on their title and abstract, followed by full-text review to determine eligibility. Data extracted from selected studies included: author(s), publication year, study model (animal or human), NSC source, transplantation method, follow-up duration, safety profiles (e.g., tumorigenesis, immunogenicity), and functional outcome measures (e.g., locomotor scores, sensory recovery).

RESULT AND DISCUSSION

Embryonic stem cells have long been recognized as one of the primary sources of pluripotent stem cells—cells that possess the ability to develop into various types of cells in the body. Due to this remarkable capability, embryonic stem cells have become a central focus in research on cell-based therapies, including in the context of treating spinal cord injury (SCI). These cells provide a strong scientific foundation for developing regenerative strategies aimed at repairing damaged neural tissue (Zeng, 2023; Li et al., 2024; Kaur, 2025).

Recently, Levi and his research team conducted a Phase 2 clinical trial to evaluate the therapeutic potential of human neural stem cells derived from fetal brain tissue, known as HuCNS-SC. This study specifically targeted patients with chronic cervical SCI. In the initial stage of the trial, six patients received stem cell transplants with varying doses, with the goal of identifying the most effective and safe dosage. Once the optimal dose was determined, it was used in a new treatment group consisting of six additional patients. This group was compared to a control group to assess the therapeutic effects more objectively (Levi et al., 2019).

The results of the study demonstrated that transplantation using HuCNS-SC is both safe and feasible, and was well tolerated by the patients. Furthermore, although still in the early stages, there were indications of motor function improvement and reduced spasticity symptoms in patients who received the therapy. These findings offer hope that neural stem cell-based therapy could become an effective approach for SCI. In line with these results, other studies involving human neural stem cells have also shown favorable safety profiles, reinforcing the potential of this approach as a regenerative therapy for spinal cord injury (Tiwari et al., 2020; Lee et al., 2022; Kaur, 2025).

Mesenchymal stromal cells, commonly known as MSCs, are a type of adult stem cell that can be obtained from various body tissues, including bone marrow. In the context of therapy for spinal cord injury (SCI), MSCs have demonstrated the ability to naturally migrate to the site of injury after transplantation. This means that once introduced into the body, these cells tend to actively move toward areas of neural damage (Tahmasebi & Barati, 2022; Liu et al., 2024; Sajjad et al., 2024).

Research has shown that the timing of MSC transplantation significantly affects the effectiveness of the therapy. Better outcomes are achieved when the transplantation is performed approximately one week after the injury, as opposed to immediately following the injury. This difference suggests that the environment around the damaged tissue changes over time, and these changes appear to influence how well MSCs can function. One of the most likely explanations for this phenomenon is the role of the immune system. The body's immune response to injury evolves gradually and likely creates a microenvironment more favorable for MSC survival and function when administered at a later stage.

However, despite observed short-term improvements, the therapeutic effects of MSCs are not permanent. That is, the benefits gained from MSC transplantation tend to diminish over time and are not yet strong enough to result in lasting functional recovery. This indicates that while MSCs hold promise as one approach for SCI therapy, more comprehensive strategies or combination therapies may be required to achieve sustainable and significant long-term effects (Shang et al., 2022).

After a person experiences a spinal cord injury (SCI), the body naturally responds with a complex inflammatory reaction. This marks the beginning of the inflammation phase, characterized by the release of various pro-inflammatory molecules such as cytokines and chemokines by immune cells. As a result of this process, the microenvironment—that is, the chemical and cellular conditions surrounding the injury site—becomes pro-inflammatory, meaning it is dominated by inflammatory activity (Xia et al., 2023).

The issue is that this pro-inflammatory microenvironment does not support the healing process, especially in the context of neural stem cell (NSC) therapy. In regenerative therapy, NSCs are expected to differentiate into new neural cells and help repair damaged nervous tissue. However, if NSCs are introduced into an environment saturated with inflammation, their ability to develop and differentiate normally is significantly impaired. In other words, the post-SCI microenvironment creates conditions that are less than ideal for NSCs to function effectively (Mu et al., 2024).

Therefore, in therapeutic approaches involving NSCs, researchers and clinicians often employ immunosuppressive regimens—administration of drugs that suppress the immune response and reduce inflammation. The goal is to transform the initially hostile and damaging microenvironment into one that is more supportive and conducive to NSC survival and function. In doing so, it is hoped that these stem cells will survive longer, differentiate properly, and contribute to the regeneration of neural tissue damaged by SCI (Cheng et al., 2016; Antonios et al., 2019).

SUMMARY

Embryonic stem cells have the ability to develop into various types of body cells, making them a central focus in cell-based therapies, including those for spinal cord injury (SCI). A Phase 2 clinical trial conducted by Levi and his team evaluated human neural stem cells (HuCNS-SC) derived from fetal brain tissue in patients with chronic cervical SCI. The results indicated that the therapy is safe, well-tolerated, and showed early signs of motor improvement and reduced spasticity.

In addition, mesenchymal stem cells (MSCs) derived from adult tissues such as bone marrow also hold potential for SCI therapy due to their ability to migrate to the site of injury. MSC transplantation is most effective when performed approximately one week after the injury. However, the benefits

are temporary and insufficient for long-term recovery.

Following SCI, the body triggers an inflammatory response that creates a microenvironment unfavorable for neural stem cells (NSCs). Therefore, NSC therapies are often accompanied by immunosuppressive drugs to reduce inflammation and create a more supportive environment for neural tissue regeneration.

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