

Review Article



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Intramedullary Neural Stem Cell Transplantation in Spinal Cord Injury: Timing, Targets, and Techniques

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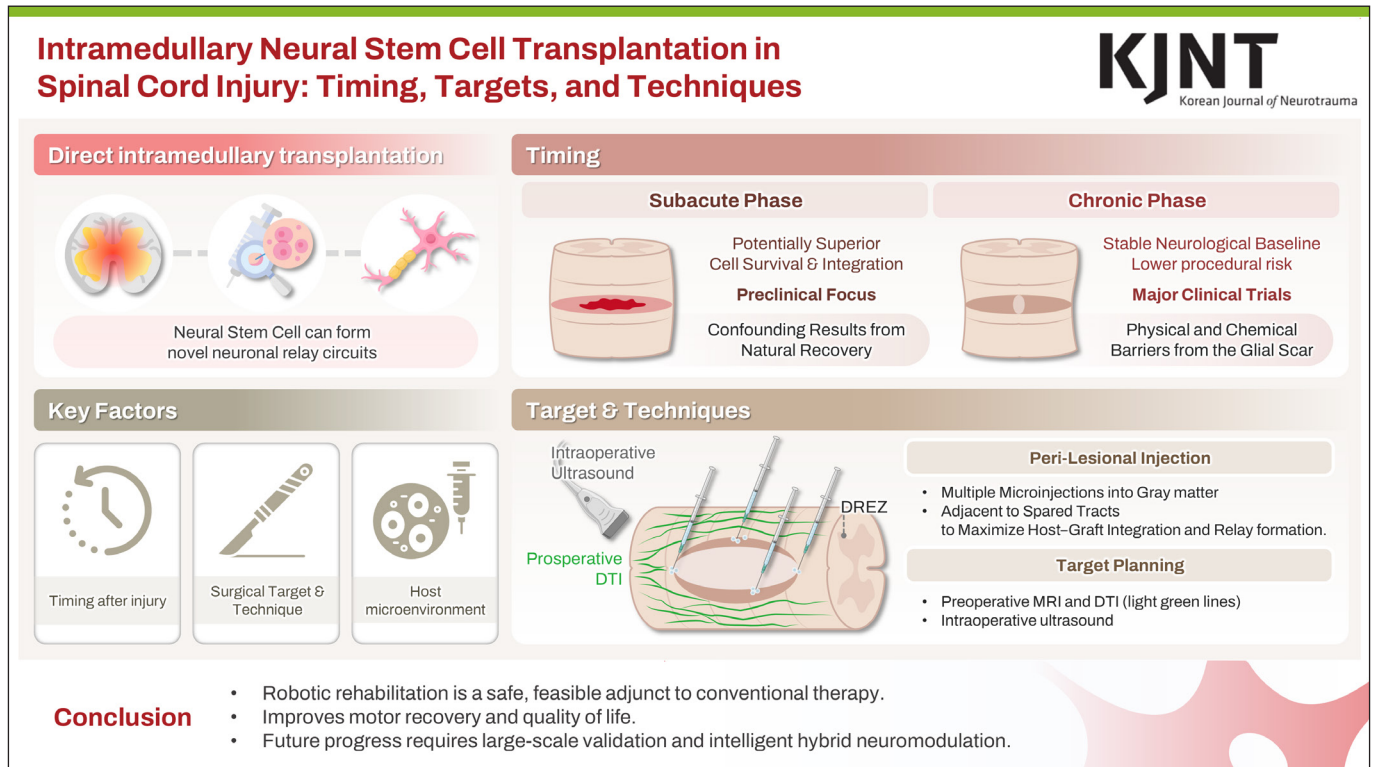
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ABSTRACT

Spinal cord injury remains one of the most challenging neurological disorders due to limited intrinsic regeneration. Neural stem cell (NSC) transplantation offers a promising strategy for restoring neural circuitry and functional recovery. Among delivery methods, direct intramedullary transplantation provides the most localized graft placement and has shown encouraging safety and efficacy in early clinical trials. This review summarizes current evidence and technical considerations for intramedullary NSC transplantation. Key factors influencing outcomes include timing after injury, cell source, surgical approach, and host microenvironment. Advances in microsurgical delivery techniques and biomaterial scaffolds have improved graft survival and integration while minimizing procedure-related risks. Clinical data demonstrate that intramedullary NSC transplantation is feasible and generally safe, with early signals of motor improvement. Nevertheless, challenges remain in achieving consistent cell engraftment and long-term functional gains. Future work should focus on refining transplantation parameters, establishing standardized surgical protocols, and conducting multicenter trials with long-term follow-up to confirm clinical efficacy. By integrating current findings, this review provides a concise overview of surgical evolution and translational progress, highlighting intramedullary NSC transplantation as a key frontier in regenerative spinal surgery.

Keywords: Spinal cord injury; Neural stem cells; Spinal cord regeneration; Cordotomy; Technique; Clinical trial

GRAPHICAL ABSTRACT



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Conflict of Interest

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Informed Consent

This study does not require informed consent.

Ethics Approval

This study does not require ethics approval.

INTRODUCTION

Spinal cord injury (SCI) leads to abrupt and often permanent loss of motor, sensory, and autonomic function.⁵⁾ Current treatments such as decompression and stabilization mainly prevent secondary damage but rarely restore function because of limited neural regeneration.^{16,18,20)}

Stem cell transplantation has been investigated as a regenerative strategy to overcome these barriers.¹⁰⁾ While various stem cell types have been investigated for SCI, including mesenchymal stem cells (MSCs) and neural stem/progenitor cells (NSCs), these represent distinct lineages. MSCs act mainly through paracrine and immunomodulatory effects, whereas NSCs possess direct neuroregenerative and circuit-forming potential. Therefore, this review focuses primarily on intramedullary transplantation of NSCs.

Donor cells can replace lost neurons and glia, remyelinate spared axons, secrete trophic factors, and modulate the immune response. In some instances, grafts may even form relay circuits that reconnect disrupted pathways.^{17,26)} Among delivery approaches, intramedullary transplantation—direct injection into the spinal cord parenchyma—maximizes graft–host apposition. This advantage comes with surgical complexity and procedural risk, yet recent clinical studies confirm its feasibility and safety.^{6,23,27,35)}

NSCs are the most clinically advanced cell type. They can generate neurons and glia, support axonal repair, and secrete trophic factors. Recent advances have made intramedullary transplantation more consistent and safer.

Despite these advances, variability in outcomes persists, largely reflecting differences in transplantation timing, target selection, and delivery technique. This review consolidates available human data and surgical experience to guide clinical application, focusing on these three determinants of success.

BIOLOGY & BRIEF RATIONALE

SCI initiates a complex and evolving pathophysiological cascade that extends far beyond the initial mechanical insult. Early vascular disruption causes ischemia and excitotoxic injury. Over subsequent hours to days, oxidative stress and mitochondrial dysfunction amplify cell loss, while activated microglia and infiltrating macrophages release inflammatory mediators that further damage spared tissue.¹⁾ In the subacute phase, reactive astrocytes proliferate and deposit extracellular matrix molecules that consolidate into a dense glial scar. This scar forms a physical and chemical barrier to axonal regrowth, while cystic cavitation enlarges the lesion core. Demyelination of spared axons further compromises conduction, contributing to long-term neurological deficits.

NSCs offer multiple avenues to counteract these barriers. They can differentiate into neurons and glial lineages, replacing lost elements of the spinal cord cytoarchitecture. NSC-derived oligodendrocytes remyelinate demyelinated axons, restoring conduction.¹⁴⁾ Beyond structural replacement, NSCs secrete trophic factors such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, which support neuronal survival, enhance plasticity, and attract host axons toward the graft.²⁵⁾ In addition, NSCs exert immunomodulatory effects by attenuating pro-inflammatory macrophage activation and promoting an anti-inflammatory milieu, thereby reducing secondary degeneration.⁷⁾

Perhaps most strikingly, NSCs can form novel neuronal relay circuits. Lu et al.²⁶⁾ demonstrated that NSC grafts in rodent models extended long-distance axons across lesions, establishing synaptic connections with host neurons. Kadoya et al.¹¹⁾ showed that these graft-derived axons received functional input and transmitted signals to appropriate distal targets. Kumamaru et al.¹⁷⁾ further confirmed corticospinal inputs into grafted NSCs, supporting the concept of excitatory relay networks capable of bridging severed pathways. Collectively, these preclinical data establish a strong biological rationale for intramedullary NSC transplantation, suggesting that grafts may not only replace damaged cells but also actively reconstitute circuit-level connectivity within the injured spinal cord.

CELL SOURCES

Sources of NSCs include fetal-derived, embryonic stem cell (ESC)-derived, induced pluripotent stem cell (iPSC)-derived lines, and more recently patient-derived induced NSCs (iNSCs) from non-invasive sources. Shin et al.³⁵⁾ reported transplantation of fetal-derived NSCs into 19 chronic cervical SCI patients, confirming safety. Curtis et al.⁶⁾ used iPSC-derived NSCs in four chronic thoracic patients. Levi et al.²⁴⁾ conducted a multicenter chronic cervical SCI NSC trial. Martin et al.²⁷⁾ provided 5-year safety follow-up data. ESC- and iPSC-derived NSCs offer scalability and standardized characteristics, though ethical and immunologic challenges remain for fetal-derived sources.

A noteworthy development from our institution concerns urine-derived human cells. Kang et al.¹²⁾ described generation of transgene-free iNSCs from human urine-derived cells using a small-molecule & self-replicating mRNA protocol. These iNSCs recapitulated key NSC features in morphology, gene expression, and multipotency (neurons, astrocytes, oligodendrocytes), and did not form teratomas in vivo. More recently, Son et al.³⁶⁾ transplanted these urine-derived iNSCs into rat SCI models; graft survival, differentiation, graft-host integration, and functional recovery (locomotor improvements) were observed. These data suggest urine-derived iNSCs may provide a patient-specific, ethically favorable, and potentially safe NSC source.

TIMING: WHEN TO TRANSPLANT

The timing of transplantation is a critical determinant of graft survival and host integration. Acute SCI is generally defined as the first ≤ 14 days after injury, a period dominated by edema, hemorrhage, and active inflammation.¹⁾ Subacute transplantation may exploit reduced inflammation and heightened plasticity, with preclinical data showing better engraftment when NSCs are delivered within weeks post-injury.³⁴⁾ However, ethical and safety concerns—including the risk of cord swelling, hemodynamic instability, and challenges in patient selection—have limited human NSC trials in this window. By contrast, oligodendrocyte progenitor cells (OPCs) have been tested subacutely with encouraging outcomes.⁹⁾ Chronic SCI is variably defined as >3 –6 months after injury; many clinical studies enroll patients at ≥ 12 months, a stage characterized by consolidated glial scarring and cystic cavitation^{6,21,23)} (**FIGURE 1**).

Most NSC human trials have therefore targeted chronic SCI due to greater lesion stability and lower procedural risk. Importantly, enrolling patients with little or no prospect of spontaneous recovery also eases ethical considerations for trial approval, since the intervention does not deprive participants of other effective treatment options. In addition, outcomes in such chronic cohorts can be interpreted with more confidence even

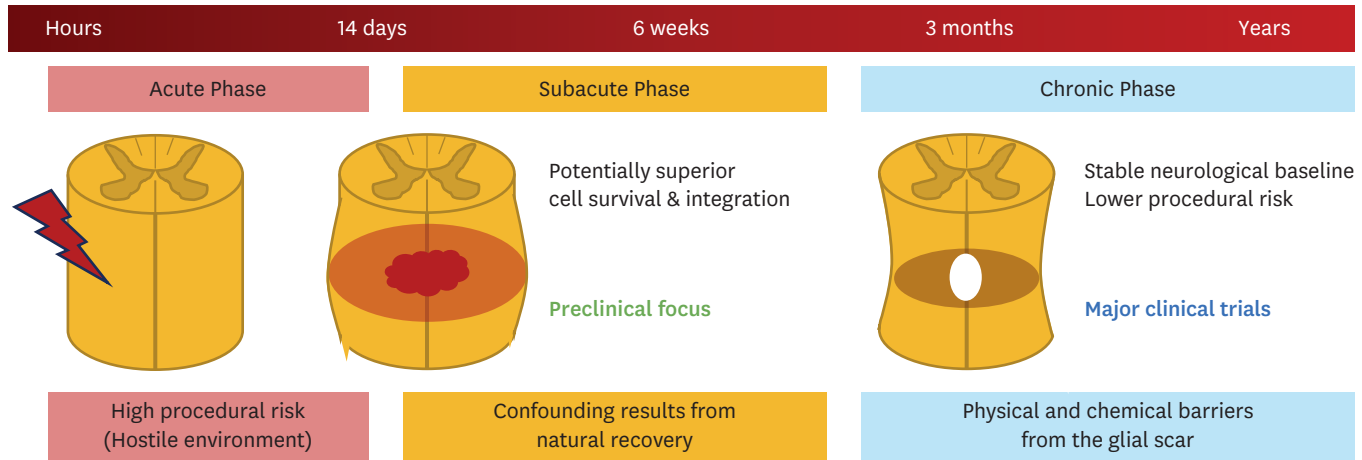


FIGURE 1. Pathophysiology of spinal cord injury across temporal phases and therapeutic implications for NSC transplantation. The schematic illustrates acute, subacute, and chronic phases following spinal cord injury. The acute phase is characterized by hemorrhage, edema, excitotoxicity, and inflammatory cell infiltration, creating a hostile environment for graft survival. The subacute phase shows partial resolution of inflammation, axonal sprouting, and extracellular matrix remodeling, representing a potentially permissive window for NSC engraftment and circuit integration. In the chronic phase, dense glial scarring, chondroitin sulfate proteoglycan deposition, and cystic cavitation predominate, stabilizing the lesion but limiting regeneration. NSC: neural stem cell.

without randomized controls, because neurological gains are unlikely to reflect natural recovery but instead suggest a treatment effect of stem cell transplantation. Shin et al.³⁵⁾ transplanted fetal-derived NSCs into chronic cervical patients safely, with some sensory improvements. Curtis et al.⁶⁾ used six-track intramedullary injections of 2 million iPSC-derived/human spinal cord-derived NSCs in chronic thoracic SCI, reporting safety and partial motor gains. Levi et al.²³⁾ expanded to 17 chronic cervical patients (4–24 months post-injury), confirming safety and modest upper-extremity improvements. Thus, while chronic transplantation remains the clinical standard, carefully designed subacute NSC trials may hold future promise.

From a biology-of-timing perspective, the acute phase is dominated by vasogenic edema, disrupted perfusion, and a surge of pro-inflammatory cytokines and excitotoxic neurotransmitters—all hostile to graft survival.¹⁾ The subacute window (from 2 to 6 weeks) is marked by partial resolution of edema and inflammation, active sprouting, and matrix remodeling before the glial scar fully consolidates; multiple preclinical studies report superior cell survival, neurite extension, and synaptic integration with transplants delivered during this interval.³⁴⁾ In contrast, the chronic milieu presents dense astroglial scarring, chondroitin sulfate proteoglycan accumulation, and cystic cavitation that impede cell dispersion and axonal growth; nonetheless, early human trials in chronic cohorts have confirmed surgical feasibility and long-term safety.^{6,23,27,35)}

Notably, preclinical studies reveal a heterogeneous picture: Cheng et al.⁴⁾ demonstrated superior outcomes with subacute transplantation compared to chronic delivery in rodent contusion models, Nguyen et al.²⁸⁾ found that immediate transplantation failed to produce functional benefits. Meanwhile, Salazar et al.³³⁾ reported locomotor recovery even after transplantation at 30 days post-injury (early chronic) in mouse models. These findings suggest that the optimal timing of NSC delivery is not yet firmly established and may depend on injury model, cell source, and host condition.

Mechanistically, the subacute phase remains attractive given reduced inflammation and heightened plasticity, coupled with evidence that NSCs can suppress neuroinflammation.⁴⁾ Nevertheless, clinical translation has thus far favored chronic cohorts to establish safety on stable neurological baselines, highlighting the gap between biological permissiveness and regulatory or ethical feasibility.

Operationally, timing also intersects with trial logistics. Acute-phase enrollment is constrained by critical care priorities, fluctuating neurologic exams, and consent challenges. Subacute enrollment requires rapid manufacturing/release testing and coordination with early rehabilitation. Chronic enrollment, by comparison, allows stable baselines, clearer risk–benefit assessments, and regulatory comfort with long-term tumorigenicity surveillance. Notably, the subacute OPC experience (21–42 days post-injury) demonstrates that intramedullary delivery, short-course immunosuppression, and safety monitoring are feasible in this time frame,⁹⁾ providing a translational template that future NSC protocols could adapt.

Finally, timing informs endpoint selection and effect-size expectations. In subacute cohorts, plasticity may enable larger gains but mandates controlled designs to disentangle treatment effects from natural recovery. In chronic cohorts, smaller absolute gains may still be clinically meaningful for independence, and improvements are less likely to be confounded

TABLE 1. Comparison of transplantation timing in spinal cord injury

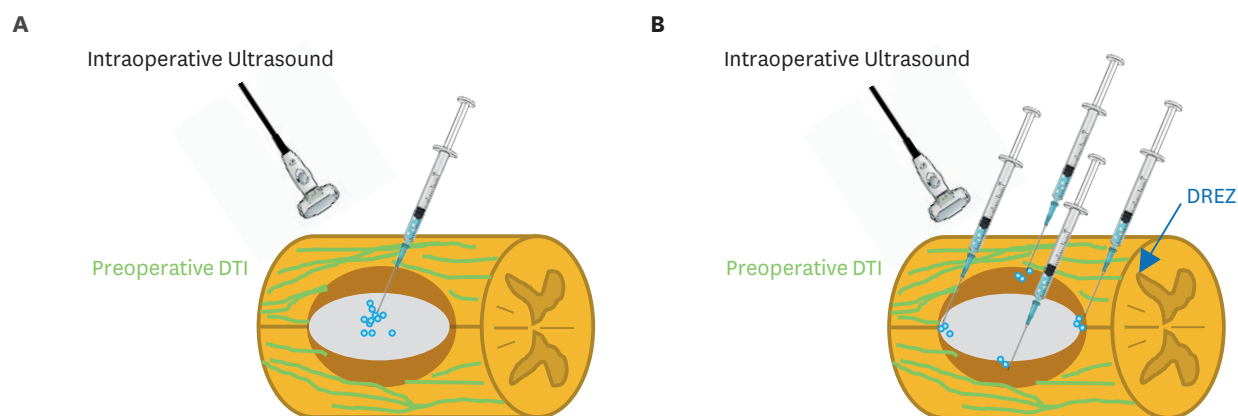
Phase	Biological environment	Advantages for transplantation	Disadvantages/challenges
Acute (≤ 14 days)	Hostile inflammatory environment, edema, hemorrhage, excitotoxicity.	Generally avoided due to high risk.	High procedural risk (swelling, instability), unstable patient condition, ethical/logistical challenges in consent and screening.
Subacute (2–6 weeks)	Resolving inflammation, heightened neuroplasticity, active tissue remodeling.	Biologically permissive environment, potentially superior cell survival, engraftment, and integration (preclinical data).	Logistical complexity (rapid cell manufacturing), potential for confounding results from natural recovery.
Chronic (> 3 –6 months)	Stable lesion, consolidated glial scar, cystic cavitation, inhibitory molecules.	Stable neurological baseline, lower procedural risk, clear assessment of treatment effect without confounding by natural recovery.	Physical and chemical barriers from the glial scar impede cell dispersion, axonal growth, and integration.

by spontaneous recovery.²⁴⁾ These considerations justify why most NSC trials have begun in chronic SCI and support a stepwise strategy: establish safety and procedural reliability chronically, then prospectively test optimized NSC products and delivery protocols in subacute windows where biology may be more permissive (**TABLE 1**).

TARGETS & SURGICAL PLANNING: WHERE TO TRANSPLANT

Targeting decisions influence both safety and efficacy. Lesion core injections aim to fill cavities but face challenges of poor vascularity and tissue fragility. Peri-lesional targeting places cells into relatively preserved gray matter adjacent to spared tracts, maximizing opportunities for relay formation. Human NSC trials have adopted peri-lesional strategies: Curtis et al.⁶⁾ used a multi-track perilesional grid, and Levi et al.²³⁾ applied similar techniques in cervical patients. Imaging is essential for planning. Preoperative magnetic resonance imaging (MRI) defines lesion morphology, while diffusion tensor imaging (DTI) maps spared corticospinal tracts. Intraoperative imaging can support targeting and depth control; frame-based MRI-guided systems and intraoperative ultrasound are practical options in selected settings.^{19,37)} Recent reviews emphasize that combining advanced imaging with peri-lesional targeting reduces iatrogenic injury and enhances graft survival.²²⁾ Cervical SCI is favored in clinical trials because even modest hand and arm recovery has profound functional implications for independence.

Additional insights can be drawn from clinical MSC transplantation trials conducted by Jeon and colleagues. In a phase III randomized trial, Oh et al.³⁰⁾ injected autologous MSCs into five intramedullary sites, comprising both the lesion cavity and proximal spared cord, and complemented this with subdural injections. Similarly, Park et al.³¹⁾ adopted a combined strategy, targeting both three tracks within the lesion cavity and two tracks in the proximal cord, while also administering subdural MSCs. The rationale was to overcome the low vascularity of the lesion core while harnessing the survival advantage of grafts placed into preserved proximal cord tissue. This dual targeting strategy exemplifies how combining lesion and peri-lesional injections can balance risks and optimize graft survival and integration. Although these studies employed MSCs, the surgical principles are directly applicable to NSC transplantation and support the concept of multi-site targeting rather than single epicenter injections (**FIGURE 2**).



Category	Rationale	Advantages	Limitations
(A) Lesion core injection	Fill the cystic cavity and reconstruct internal support	• Direct replacement of lost tissue • Simple posterior access • Allows larger injection volume	• Poor vascularity → low graft survival • Fragile cavity wall → leakage risk • Limited host-graft integration
(B) Peri-lesional injection	Target viable gray matter adjacent to spared tracts Especially near the DREZ to maximize graft integration	• Better vascularity and graft survival • Close to functional tracts → promotes relay formation • Reduced risk of necrosis	• Technically demanding • Limited injection volume per track • Requires precise navigation to avoid dorsal column injury

FIGURE 2. Injection targets schematic. Intramedullary injection targets in spinal cord injury. (A) Lesion core injection: the needle tip enters the cystic cavity to deposit a cell suspension that fills the core; this approach may encounter unstable parenchyma and poor vascularity. (B) Peri-lesional injection: multiple microinjections into preserved gray matter adjacent to spared tracts (e.g., corticospinal tract and the DREZ) to maximize host-graft integration and relay formation. Target planning is informed by preoperative MRI and DTI (light green lines) and can be refined with intraoperative ultrasound or MRI guidance. Exemplary human protocols have used multi-track Hamilton syringe delivery near lesion margins in thoracic and cervical cohorts. DREZ: dorsal root entry zone, MRI: magnetic resonance imaging, DTI: diffusion tensor imaging.

TECHNIQUES OF INTRAMEDULLARY DELIVERY: HOW TO TRANSPLANT

Delivery technique is the cornerstone of successful NSC transplantation. Most trials use laminoplasty or laminectomy, durotomy, and controlled pial entry. Myelotomy is limited to essential access, minimizing cord manipulation. Delivery devices have evolved: early free-hand stabilization has been complemented by stereotactic injectors and floating cannula systems that compensate for cord pulsation.⁸⁾ Such precision platforms reduce shear stress and standardize injection depth, improving safety.²²⁾ Most human NSC trials employ Hamilton syringes, which allow precise low-volume infusion. Needle gauges of 27–30 G are commonly used. Butterfly needles are not reported in human intramedullary NSC studies, though animal models have tested them, raising concerns of reflux and tissue injury. Injection schema vary: Shin et al.³⁵⁾ used multiple cervical injection sites, while Curtis et al.⁶⁾ performed six-track injections in thoracic SCI. Multi-track injections distribute cells across lesion borders but increase technical complexity. Infusion rates and dwell times are underreported in human studies; animal research supports slow infusion (0.5–1 $\mu\text{L}/\text{min}$), small volumes (10–20 μL), and 2–5 minutes dwell to reduce reflux.³⁴⁾ Curtis reported 2 million cells total, approximately 300,000 per track.⁶⁾ In MSC trials, per-site volumes around 0.2 mL were delivered over short intervals with brief dwell and pial sealing.^{30,31)} For NSCs, preclinical data favor smaller per-track volumes (10–20 μL) and slow rates (0.5–1 $\mu\text{L}/\text{min}$) to limit reflux and shear.³⁴⁾ Fibrin glue was applied to the pial entry site to prevent reflux. Oh et al. used

TABLE 2. Technical parameters in intramedullary stem cell delivery

Parameter	Typical approach	Evidence/notes	Reference
Surgical exposure	Laminoplasty or laminectomy with durotomy	Ensures safe access to cord	Shin et al. (2015) ³⁵⁾
Cord entry	Limited myelotomy, avascular pial entry	Minimizes manipulation	Park et al. (2012) ³¹⁾ ; Oh et al. (2016) ³⁰⁾
Injection device	Hamilton syringe (manual), stereotactic injector, floating cannula	Hamilton syringe = standard; floating cannula reduces shear stress	Curtis et al. (2018) ⁶⁾ ; Federici et al. (2021) ⁸⁾ ; Lee et al. (2022) ²²⁾
Needle gauge	27–30 G	Reported in most animal studies and clinical use	Shin et al. (2015) ³⁵⁾
Infusion rate	0.5–1 μ L/min	Animal data suggest slower infusion improves survival	Salewski et al. (2015) ³⁴⁾
Volume per site	10–20 μ L (NSCs); 0.2 mL (MSC trials)	MSC trials (Oh, Park); NSC animal data favor smaller volumes	Oh et al. (2016) ³⁰⁾ ; Park et al. (2012) ³¹⁾ ; Salewski et al. (2015) ³⁴⁾
Dwell time	2–5 minutes	Reduces reflux	Salewski et al. (2015) ³⁴⁾
Pial sealing	Fibrin glue	Applied to prevent reflux	Oh et al. (2016) ³⁰⁾
Monitoring	Intraoperative neurophysiology (MEP, SEP, EMG); hemodynamic stability	Used variably across trials	Yamazaki et al. (2020) ³⁹⁾

NSC: neural stem cell, MSC: mesenchymal stem cell, MEP: motor evoked potential, SEP: somatosensory evoked potential, EMG: electromyography.

a nearly identical schema in their phase III trial, standardizing injections across centers to five tracks intramedullary plus subdural infusion.³⁰⁾ Both studies emphasized the importance of selecting avascular cord entry points, minimizing cord manipulation, and sealing entry sites. They also highlighted perioperative strategies, including stable mean arterial pressure, controlled ventilation to limit cord motion, and early postoperative rehabilitation as integral parts of the delivery protocol.

Although performed with MSCs, these surgical details offer a template for best practice in NSC transplantation: Hamilton syringe–based multi-track injections at controlled rates and depths, combined with careful sealing and physiological monitoring. In addition, neurophysiological monitoring such as motor evoked potential (MEP) and electromyography has been frequently employed in clinical stem cell trials for SCI as an outcome assessment tool.³⁹⁾ Collectively, these lessons underscore that meticulous technical execution—down to needle gauge, infusion speed, and sealing technique—is essential for safe and effective intramedullary NSC delivery (TABLE 2).

CLINICAL EVIDENCE IN HUMANS

Four major human NSC trials shape current understanding. Shin et al.³⁵⁾ transplanted fetal-derived NSCs into 19 chronic cervical patients, showing feasibility and safety, with some sensory improvements. Curtis et al.⁶⁾ transplanted iPSC-derived NSCs into four chronic thoracic patients, delivering six-track Hamilton syringe injections; 2 patients exhibited motor improvement. Levi et al.²³⁾ extended the approach to 17 chronic cervical patients, reporting safety and modest gains in upper-extremity motor scores. Martin et al.²⁷⁾ provided long-term safety data, showing no tumorigenesis at 5 years. Across these studies, safety is consistently supported, but efficacy signals remain variable and modest. Limitations include small sample sizes, lack of controls, and underreporting of technical parameters. Nevertheless, these trials demonstrate the feasibility of intramedullary NSC transplantation and underscore the need for larger, controlled studies to establish efficacy.

PATIENT SELECTION & ENDPOINTS

Cervical SCI patients, particularly American Spinal Injury Association Impairment Scale (AIS) A/B, are prioritized for NSC trials due to the profound functional significance of even modest upper-limb recovery. Gains of only a few points in the Upper Extremity Motor Score can substantially improve independence in activities of daily living. Consequently, most human NSC trials have enrolled chronic cervical cohorts. More recent protocols have also explored the inclusion of AIS C patients to evaluate broader applicability, reflecting a trend toward expanding eligibility while maintaining safety margins.

The clinical studies by Jeon's group further highlight practical considerations in patient selection. In their phase I/II and phase III MSC trials, inclusion criteria were limited to traumatic SCI patients with AIS A or B status, stable neurological deficits for at least 12 months, and no evidence of progressive neurological decline.^{30,31} Exclusion criteria included severe systemic illness, coagulopathy, active infection, or spinal instability requiring further surgery. This strategy ensured homogeneity of baseline deficits and reduced confounders from spontaneous recovery.

Endpoints in Jeon's studies extended beyond standard International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) motor and sensory scores to include electrophysiological testing (MEP, somatosensory evoked potential), MRI and DTI imaging, spasticity scales, bladder and bowel function, and validated quality of life questionnaires. DTI metrics (e.g., FA) correlate with tract integrity and clinical state in chronic SCI and can serve as mechanistic secondary endpoints.^{32,38} More recent NSC protocols have incorporated multidimensional endpoints such as SCIM and GRASSP, which provide sensitive evaluation of independence and fine-motor recovery. Long-term endpoints, as highlighted by the 5-year follow-up of Martin et al.,²⁷ are also essential to capture delayed safety signals and durable functional gains. Importantly, both Jeon's MSC trials and subsequent NSC studies emphasized the integration of rehabilitation programs post-transplantation, recognizing that functional recovery requires both biological and rehabilitative inputs.

In addition to these completed early-phase studies, one actively recruiting trial is underway in South Korea (NCT04812431).²⁹ This single-center, open-label phase I/IIa study, led by S.Biomedics in collaboration with Yonsei University, is testing PSA-NCAM(+) neural precursor cells derived from human ESCs in patients with subacute, complete cervical SCI (AIS A, C4–C7). Patients are enrolled between 7 and 60 days post-injury. The primary endpoints focus on safety, including adverse events, clinical and laboratory findings, and physiological monitoring up to 72 weeks post-transplantation. Secondary outcomes include graft survival on MRI, immunologic rejection assays, and functional measures such as ISNCSCI motor/sensory scores, pain scales, and SCIM.²⁹ This ongoing trial exemplifies the shift toward carefully designed subacute studies with clearly defined endpoints, aiming to bridge the gap between preclinical permissive biology and clinical feasibility.

REGULATORY/ETHICAL CONSIDERATIONS

NSC production for clinical use requires compliance with Good Manufacturing Practice standards, including sterility assurance, genomic stability, and potency assays for

differentiation potential. Regulatory oversight is particularly stringent. In Korea, the Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products (enforced by the Ministry of Food and Drug Safety in 2020) mandates Institutional Review Board approval, designation of qualified institutions, long-term patient follow-up, and national registry-based monitoring for all regenerative medicine therapies.^{15,40)} The U.S. Food and Drug Administration and the European Medicines Agency impose similar requirements regarding batch release, traceability, and adverse event reporting. Internationally, harmonization with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice and World Health Organization frameworks has been emphasized to avoid regulatory fragmentation and to ensure comparability across jurisdictions.⁴¹⁾

Ethical concerns remain central. While fetal-derived NSCs raise issues regarding tissue sourcing, iPSC-derived NSCs mitigate some of these controversies. Regardless of origin, informed consent must explicitly address potential risks such as tumorigenesis, ectopic tissue formation, and long-term immunosuppression. Tumorigenicity surveillance is particularly emphasized, with many frameworks requiring decades-long follow-up and dedicated patient registries.^{40,41)} Ethical discussions also extend to the problem of unregulated cross-border “stem cell tourism,” highlighting the importance of transparent and internationally harmonized governance.²⁾ In Korea, the regulatory framework explicitly classifies stem cell transplantation for SCI as a “high-risk” regenerative therapy, requiring ministerial approval, enhanced safety monitoring, and structured long-term surveillance before and after clinical use.¹⁵⁾ This categorization reflects both the invasive nature of intramedullary delivery and the uncertainty of long-term outcomes, and it sets a precedent for how NSC clinical trials must be designed to ensure patient safety.

FUTURE DIRECTIONS

Early human studies of intramedullary transplantation have been pioneering but limited—small, heterogeneous, and designed mainly to prove feasibility rather than efficacy. Moving toward clinical adoption will require stricter methodology and shared technical standards.

Delivery techniques must be standardized across centers, including exposure, pial entry, needle gauge, track number, infusion parameters, and sealing methods. These details are rarely reported yet critically influence graft survival and clinical interpretation. To enhance reproducibility, future protocols should include prespecified surgical manuals, intraoperative monitoring, imaging guidance, and unified postoperative care guidelines.

Beyond technique, product optimization remains a priority. Combining stem cell transplantation with hydrogels or bioengineered scaffolds can improve graft survival and host integration by providing mechanical protection and trophic support.^{3,13)} Integration with task-specific rehabilitation and neuromodulation may further promote plasticity and functional recovery. Emerging tools such as robotic injectors could also improve procedural accuracy in multi-track delivery.

Ethically robust trial design is essential. For chronic SCI—where spontaneous recovery is minimal—multicenter studies with harmonized endpoints and long-term follow-up are needed. For subacute cases—where biological permissiveness is higher—risk mitigation and

independent safety oversight are required. Common data elements, prospective registries, and transparent reporting will accelerate learning across institutions. Ultimately, large multicenter randomized trials with standardized protocols are needed to demonstrate efficacy and establish best practices.

CONCLUSIONS

Intramedullary transplantation of neural stem cells is now a practical and safe surgical procedure.

However, clear evidence of functional recovery is still lacking. Future studies should use strict methods and ethical control to confirm the real effect of this therapy. This review provides simple surgical guidance on timing, target, and delivery. Standardized techniques and cooperative multicenter trials will be key to proving efficacy and bringing stem cell therapy into regular clinical use.

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