

Intrathecal Stem Cell and Cell-Based Therapies for Spinal Cord Injury: Delivery Methods, Dose Optimization, and Translational Gaps Abstract

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ABSTRACT

Spinal cord injury (SCI) remains one of the most devastating neurological disorders, characterized by irreversible neuronal loss, demyelination, and glial scar formation. Conventional pharmacological and surgical approaches offer limited restoration of function, leading to an increasing emphasis on regenerative strategies. Among these, intrathecal stem cell and cell-based therapies have emerged as promising interventions capable of modulating the local microenvironment, promoting axonal regeneration, and enhancing neuroprotection. This review critically examines the evolving landscape of intrathecal delivery of mesenchymal stem cells (MSCs), neural stem cells (NSCs), and related cell-based platforms in SCI management. It focuses on delivery methodologies, dose optimization strategies, and the translational barriers impeding clinical success. Comparative evidence from animal models and clinical trials indicates that intrathecal administration facilitates more targeted biodistribution and reduced systemic adverse events compared to intravenous routes. Recent advances in hydrogel scaffolds, exosome-based therapies, and gene-edited cell lines further expand the therapeutic potential of this approach. However, inconsistencies in dosing protocols, cell characterization, and outcome metrics continue to hinder clinical translation. This review synthesizes data from 40 recent peer-reviewed studies and clinical trials (2022–2025) to identify current gaps, optimize delivery paradigms, and propose directions for future translational research. Ultimately, intrathecal stem cell therapy represents a dynamic frontier in neuroregenerative medicine, poised to transform SCI rehabilitation once standardization and long-term safety are achieved.

Keywords: Spinal cord injury, Intrathecal stem cell therapy, Mesenchymal stem cells, Neural stem cells, Cell-based therapy, Regenerative medicine

I. INTRODUCTION

Spinal cord injury (SCI) is one of the most devastating neurological conditions, leading to either partial or complete loss of sensory, motor, and autonomic functions below the site of the lesion. Globally, it affects an estimated 40 to 80 individuals per million every year, with most cases resulting from traumatic incidents such as road traffic accidents, falls, or acts of violence. Beyond its severe physical consequences, SCI also places a significant psychological and socioeconomic strain on patients, their families, and the healthcare system. Although modern medicine has made substantial progress in areas such as emergency response, surgical decompression, and rehabilitation, the full restoration of lost neurological function remains an unsolved challenge. This limitation primarily arises from the central nervous system's (CNS) poor ability to regenerate once damaged.

The progression of SCI occurs in two main phases. The **primary injury** phase involves the immediate mechanical damage to neural and glial cells, along with bleeding and disruption of blood flow in the spinal cord. This initial trauma triggers a **secondary injury cascade**, characterized by inflammation, oxidative stress, apoptosis (programmed cell death), and the formation of a glial scar — a dense barrier that obstructs axonal regeneration. These overlapping events create a highly hostile environment that prevents the natural repair of nerve tissue. Conventional pharmacological treatments, such as high-dose methylprednisolone, have shown limited effectiveness and often come with significant adverse effects. Consequently, scientific attention has shifted toward regenerative therapeutic approaches that focus on rebuilding damaged

neural networks, controlling inflammation, and supporting functional recovery.

Among these regenerative approaches, **stem cell and cell-based therapies** have emerged as highly promising strategies. These therapies utilize cells capable of differentiating into various neural lineages and supporting tissue repair. Commonly studied cell types include **mesenchymal stem cells (MSCs)**, **neural stem cells (NSCs)**, and **induced pluripotent stem cells (iPSCs)**. They can be derived from the patient's own body (autologous) or from a donor (allogeneic). These cells not only have the potential to replace damaged neurons but also secrete growth factors, modulate immune responses, and create a more favorable environment for regeneration.

A particularly advantageous method of administering these therapeutic cells is through the **intrathecal route**, where cells are injected directly into the **cerebrospinal fluid (CSF)**. This technique allows the transplanted cells to reach the injured area more efficiently, bypassing the **blood-brain barrier (BBB)**—a natural defense mechanism that often restricts the entry of therapeutic agents into the CNS. Additionally, intrathecal administration minimizes systemic exposure, thereby reducing potential side effects associated with other delivery routes such as intravenous injection. Over the last decade, several preclinical experiments and early-stage clinical trials have demonstrated that intrathecal stem cell delivery is both **feasible and generally safe**, although the results regarding functional improvement have varied across studies.

Despite these encouraging findings, several **translational challenges** continue to hinder clinical progress. The lack of consistency in parameters such as **cell type, dosage, frequency, and timing** of administration has made it difficult to compare outcomes across studies. Furthermore, differences in **patient selection criteria, assessment tools, and follow-up duration** have contributed to inconsistencies in reported efficacy. Ethical and regulatory concerns surrounding stem cell sourcing, manipulation, and use further complicate large-scale clinical implementation. Therefore, there is an increasing consensus within the scientific community that future research must focus on **standardizing treatment protocols, optimizing dosage and delivery, and understanding underlying mechanisms** to bridge the gap between laboratory success and real-world clinical benefit.

In this context, the present review aims to provide a comprehensive and critical overview of

current evidence related to **intrathecal stem cell and cell-based therapies in spinal cord injury**. It examines the various **delivery techniques**, evaluates **dose optimization strategies**, and highlights **translational limitations** that must be addressed to move these therapies closer to clinical reality. By analyzing findings from around **40 recent peer-reviewed studies**, this article seeks to identify major trends, clarify ongoing controversies, and propose evidence-based recommendations for future investigations. Ultimately, the goal is to guide the scientific community toward more effective and standardized clinical applications of stem cell therapy in spinal cord injury recovery.

II. METHODOLOGY

This review followed a **structured narrative approach** designed to provide an in-depth yet flexible examination of the available evidence on intrathecal stem cell and cell-based therapies for spinal cord injury (SCI). The goal was to achieve a comprehensive understanding of the topic while maintaining the adaptability to include newly emerging findings. The review process was conducted in line with widely accepted biomedical literature review standards, ensuring that the study remained transparent, reproducible, and relevant to both researchers and clinicians.

2.1 Literature Search Strategy

A detailed and systematic search was conducted across several major biomedical databases—**PubMed, Scopus, Web of Science, and ClinicalTrials.gov**—to identify relevant studies. The search covered research published between **January 2015 and October 2025**, ensuring the inclusion of the most up-to-date data in this rapidly evolving field.

To capture a wide scope of evidence, both **Medical Subject Headings (MeSH)** and free-text keywords were used in various combinations. Key terms included “spinal cord injury,” “intrathecal injection,” “stem cell therapy,” “cell-based therapy,” “mesenchymal stem cells,” “neural stem cells,” “exosomes,” “dose optimization,” and “delivery methods.” Logical operators such as **AND** and **OR** were used strategically to balance the sensitivity and specificity of the search results.

The search was limited to **English-language publications** and focused on studies conducted in **humans or mammalian models** to ensure clinical relevance. References from selected papers were also screened manually to identify

additional eligible studies that may not have appeared in the initial database searches.

2.2 Inclusion and Exclusion Criteria

The selection of studies was guided by predefined inclusion and exclusion criteria to ensure methodological rigor and relevance.

Inclusion criteria:

- Experimental or clinical studies investigating the **intrathecal or cerebrospinal delivery** of stem cells or their derivatives in spinal cord injury.
- Research reporting outcomes related to **efficacy, safety, biodistribution, or underlying mechanisms** of action.
- **Randomized controlled trials (RCTs), cohort studies, preclinical animal studies, systematic reviews, and meta-analyses** published in peer-reviewed journals.

Exclusion criteria:

- Studies using only **intravenous** or **intraparenchymal** delivery routes.
- **Conference abstracts, letters to the editor, or non-peer-reviewed reports.**
- **Duplicate publications** or studies lacking measurable qualitative or quantitative outcomes.

This filtering process ensured that only high-quality and scientifically sound studies were included in the final synthesis.

2.3 Data Extraction and Synthesis

Data from each eligible study were systematically compiled into structured tables. These tables summarized essential information such as **cell type and source, dosage, delivery method, follow-up duration, and reported outcomes**—both functional and molecular. Clinical outcomes of particular interest included **American Spinal Injury Association (ASIA) scores, motor and sensory improvements, and biomarker analyses** that provided insight into the biological response following treatment.

Whenever possible, findings from **animal models** were compared with results from **human clinical trials** to assess the degree of translational alignment between preclinical and clinical outcomes. Due to the diversity in study designs, cell types, and outcome measures, a **narrative synthesis** approach was used instead of a quantitative meta-analysis. This allowed for a

detailed comparison of emerging patterns and therapeutic trends across the included literature.

2.4 Quality Assessment

To ensure that the evidence synthesized in this review was methodologically sound, a structured quality assessment was carried out for both clinical and preclinical studies.

- For **clinical trials**, the **Cochrane Risk of Bias Tool** was employed to evaluate aspects such as randomization, blinding, outcome reporting, and the completeness of follow-up data.
- For **animal studies**, the **SYRCLE's Risk of Bias Tool** (Systematic Review Centre for Laboratory animal Experimentation) was applied to assess similar parameters relevant to preclinical research.

Each study was independently reviewed by multiple assessors to maintain objectivity. Any disagreements regarding bias classification or study quality were resolved through discussion and consensus to ensure accuracy and consistency.

2.5 Scope and Limitations

This article represents a **comprehensive narrative review** rather than a formal systematic review. It synthesizes data from approximately **40 peer-reviewed studies**, encompassing both experimental and clinical research on intrathecal stem cell and cell-based therapy for SCI.

While every effort was made to include all relevant literature, the review acknowledges certain limitations. Some **unpublished or non-English studies** may not have been captured, potentially omitting valuable data. Additionally, because of the heterogeneity across study designs, a formal meta-analysis was not feasible.

Nevertheless, the current selection of studies offers a representative overview of global research trends, clinical advancements, and ongoing challenges in the field. This structured synthesis provides an evidence-based foundation for future investigations aimed at refining delivery protocols, improving dosing strategies, and enhancing translational outcomes in spinal cord injury therapy.

III. DISCUSSION / MAIN BODY

a. Pathophysiology and Mechanistic Rationale

Spinal cord injury (SCI) is a multifaceted pathological event that leads to a cascade of destructive biological processes, ultimately resulting in the loss of motor, sensory, and

autonomic functions. The initial or primary phase of injury is caused by mechanical trauma that directly damages neuronal axons, glial cells, and the surrounding vasculature. This mechanical insult triggers a secondary phase characterized by a complex biochemical and cellular cascade, including oxidative stress, excitotoxicity, lipid peroxidation, inflammation, and glial scar formation, all of which exacerbate neural tissue destruction and impede recovery.

Following SCI, the microenvironment within the spinal cord becomes highly hostile to regeneration. This environment is marked by the infiltration of immune cells such as macrophages and microglia, along with the excessive release of inflammatory cytokines including TNF- α , IL-1 β , and IL-6. Additionally, the accumulation of reactive oxygen species (ROS) and the breakdown of the blood–spinal cord barrier (BSCB) contribute to cellular edema and further neuronal loss. Over time, astrocytes proliferate and secrete chondroitin sulfate proteoglycans (CSPGs), forming a dense glial scar that both mechanically and chemically blocks axonal growth.

Stem cell–based therapies are designed to counteract these damaging processes and promote regeneration. Mesenchymal stem cells (MSCs) secrete neurotrophic and angiogenic factors such as BDNF, NGF, and VEGF, which support neuroprotection, vascular repair, and synaptic remodeling. Neural stem cells (NSCs) have the ability to differentiate into multiple neural lineages, including neurons, astrocytes, and oligodendrocytes, thereby facilitating remyelination and re-establishing lost neural circuits. Induced pluripotent stem cells (iPSCs)—generated from adult somatic cells—offer a personalized and immunocompatible approach for neural repair by minimizing rejection risks.

Delivering these cells via the intrathecal route—that is, directly into the cerebrospinal fluid (CSF) through a lumbar puncture—allows targeted access to the spinal cord while bypassing systemic barriers such as the blood–brain barrier (BBB). The CSF serves as a natural conduit for distributing cells along the central nervous system, enhancing their migration to injury sites. Preclinical studies have shown that intrathecal administration leads to higher cell survival rates and improved homing compared with systemic delivery. Moreover, this method is minimally invasive and avoids complications associated with direct parenchymal injections, such as hemorrhage or additional trauma.

The therapeutic rationale for intrathecal stem cell delivery is built upon three key mechanisms:

1. Cell replacement, through the integration of transplanted cells to replenish lost neural and glial populations.
2. Paracrine signaling, involving the secretion of trophic and anti-inflammatory factors that foster endogenous repair.
3. Neuroprotection, aimed at preserving remaining neural tissue and preventing further degeneration.

b. Epidemiology and Burden of Spinal Cord Injury

Spinal cord injury remains a significant global health issue, affecting an estimated 27 million people worldwide, with an annual incidence of 250,000–500,000 new cases. The burden is disproportionately higher in low- and middle-income countries, where road traffic accidents and falls are major causes. Men between the ages of 20 and 40 account for nearly 70–80% of all cases. While most injuries are traumatic, non-traumatic causes such as infections, tumors, and degenerative spinal conditions represent around 30% of total cases.

Beyond physical impairment, SCI has profound socioeconomic and psychological implications. In high-income countries, the lifetime cost per patient may exceed two million U.S. dollars, accounting for long-term medical care, assistive devices, and rehabilitation. Patients frequently experience depression, anxiety, and social isolation, which further reduce their quality of life and complicate recovery.

Chronic SCI, marked by extensive glial scarring and cyst formation, exemplifies the central nervous system's limited capacity for spontaneous repair. Traditional therapies focus primarily on preventing complications rather than promoting true regeneration. Thus, the advent of stem cell–based regenerative therapies represents a paradigm shift—from symptom management to active tissue repair and neural restoration.

c. Clinical Presentation and Classification

The clinical outcomes of SCI depend largely on both the level and completeness of the lesion. Injuries at the cervical level often cause quadriplegia, while those at thoracic or lumbar levels typically result in paraplegia. The American Spinal Injury Association (ASIA) Impairment Scale (AIS) remains the gold standard for

neurological evaluation, grading injury severity from A (complete) to E (normal function).

In the acute phase, patients may exhibit spinal shock, hypotension, and complete motor and sensory loss below the lesion. As the condition evolves, chronic symptoms such as spasticity, neuropathic pain, autonomic dysreflexia, and bladder dysfunction often develop. Magnetic resonance imaging (MRI) remains the diagnostic tool of choice, allowing visualization of hemorrhage, edema, and spinal cord compression.

The chronic stage is characterized by axonal demyelination, cyst formation, and persistent inflammation, creating an environment highly resistant to axonal regeneration. Consequently, many clinical trials focus on subacute or early chronic phases, where residual neural plasticity increases the likelihood of successful stem cell integration and repair.

d. Current Therapies and Their Limitations

Present-day management of SCI primarily focuses on stabilization, prevention of secondary damage, and functional rehabilitation. Acute interventions commonly include surgical decompression, maintenance of spinal alignment, and administration of high-dose corticosteroids such as methylprednisolone, although their neuroprotective efficacy remains controversial.

Neurorehabilitation plays a critical role in improving independence through physical therapy, functional electrical stimulation, and robot-assisted training, but it cannot replace lost neurons or restore full function. Trials investigating pharmacological agents like Riluzole and Minocycline have produced mixed or modest results.

Given these limitations, the focus has increasingly shifted to regenerative strategies—including cell transplantation, gene therapy, and biomaterial scaffolds. Among these, stem cell-based approaches are the most extensively studied, offering the potential for neuroprotection, remyelination, and synaptic repair through their multifactorial mechanisms.

e. Novel and Emerging Cell-Based Approaches Mesenchymal Stem Cells (MSCs):

MSCs derived from bone marrow, adipose tissue, or umbilical cord are among the most widely studied for SCI due to their ease of harvest, immune compatibility, and trophic factor secretion. Clinical trials have reported improvements in ASIA motor scores, sensory recovery, and bladder control

following repeated intrathecal MSC infusions. A Phase I/II trial (NCT04205019) demonstrated that umbilical cord-derived MSCs are safe and associated with modest yet sustained functional gains. Optimal dosing appears to range between $1-2 \times 10^6$ cells/kg, beyond which efficacy plateaus and inflammatory reactions may increase.

Neural Stem Cells (NSCs):

NSCs can differentiate into neurons and glial cells, enabling repair of damaged circuits. Intrathecal NSC transplantation has been shown to promote remyelination and synaptic reconnection in preclinical models. A Phase I clinical trial (The Lancet Neurology, 2023) in cervical SCI patients confirmed both safety and measurable upper-limb motor improvement.

Induced Pluripotent Stem Cells (iPSCs):

iPSCs, reprogrammed from adult somatic cells, circumvent ethical concerns tied to embryonic sources. Their autologous nature reduces rejection risk, and gene-editing technologies now allow the expression of neurotrophic factors to boost regenerative outcomes. However, tumorigenic potential and differentiation instability remain safety hurdles requiring long-term monitoring.

Oligodendrocyte Progenitor Cells (OPCs):

OPCs are essential for remyelinating surviving axons. Intrathecal delivery of OPCs in animal models has shown restoration of conduction velocity and improved locomotor outcomes. Combining OPCs with MSCs or NSCs may offer synergistic benefits.

Exosome-Based and Gene-Modified Therapies:

Cell-free approaches using extracellular vesicles (EVs) or exosomes mimic the paracrine effects of stem cells without the risk of immune rejection. Exosomes enriched with microRNA-124 or neurotrophins have demonstrated enhanced neuronal survival. Gene-modified stem cells, engineered via CRISPR/Cas9, can overexpress regenerative molecules such as BDNF and NT-3, amplifying therapeutic potency.

3D Bioprinting and Biomaterials:

Advancements in tissue engineering have enabled the creation of 3D bioprinted scaffolds embedded with stem cells, which replicate native spinal tissue architecture. Hydrogels and bioactive matrices prolong cell survival and enhance

integration with host tissue, improving long-term outcomes in experimental models.

f. Comparative Analysis of Delivery Routes and Dosing Strategies

Delivery Routes:

Stem cells can be administered through intravenous, intraspinal, or intrathecal routes. Intravenous delivery is the least invasive but results in poor CNS bioavailability due to pulmonary trapping. Intraspinal injections, though precise, carry risks of additional neural trauma. Intrathecal delivery offers an optimal balance—being minimally invasive yet capable of wide CNS distribution via the CSF. Studies consistently show higher engraftment and better functional outcomes with intrathecal administration compared to intravenous delivery. The most common side effects are mild, including transient headache or back pain.

Dosing Strategies:

The effectiveness of stem cell therapy is dose-dependent but follows a saturation curve, beyond which benefits do not increase. Preclinical evidence suggests optimal recovery at approximately 1×10^6 cells per subject, while higher doses may provoke inflammatory responses. Clinically, doses between 10–100 million cells per session, repeated every 2–3 months, have yielded encouraging results. Multiple administrations appear to sustain neuroprotection and improve long-term functional outcomes without added safety risks. However, inter-trial variability in dosage, cell preparation, and patient factors complicates standardization.

Adjunctive Approaches:

Combining stem cell therapy with rehabilitation protocols, neurotrophic factors, or biomaterial scaffolds enhances recovery. Physical training post-transplantation improves synaptic plasticity and promotes better integration of transplanted cells. Advanced imaging techniques such as MRI and PET are increasingly used for non-invasive tracking of transplanted cells, providing valuable insight into biodistribution and survival.

g. Challenges, Limitations, and Translational Gaps

Despite notable progress, several barriers hinder the widespread clinical translation of intrathecal stem cell therapy:

1. Heterogeneity of Study Design:

Considerable variation exists across studies in terms of injury severity, timing of intervention, and outcome measures. The absence of standardized metrics for sensory and autonomic recovery reduces comparability. Recent consensus guidelines emphasize uniform reporting to enhance reproducibility.

2. Poor Cell Survival and Integration:

The post-injury environment remains hostile due to ongoing inflammation and hypoxia, leading to limited long-term engraftment. Research is now focused on bioengineered scaffolds, preconditioning, and immunomodulation to enhance cell persistence.

3. Immune and Safety Concerns:

Allogeneic transplantation carries risks of rejection and tumorigenesis. Long-term data beyond two years are scarce, underscoring the need for extended surveillance and standardized regulatory frameworks.

4. Dose Optimization and Manufacturing Issues:

Producing large quantities of clinical-grade stem cells that retain viability and potency remains difficult. Batch variability, cell aging, and high production costs further complicate consistency and scalability.

5. Regulatory and Ethical Challenges:

The global regulatory landscape for cell therapy remains inconsistent. Unregulated clinics offering unproven treatments pose ethical and safety concerns, emphasizing the need for internationally harmonized guidelines.

6. Translational Disconnect:

Preclinical rodent models fail to fully replicate the chronic, complex nature of human SCI. Bridging this gap requires large-animal models, multicenter collaboration, and long-term follow-up trials.

7. Economic and Accessibility Barriers:

Stem cell therapy is costly and resource-intensive, limiting access in low-resource regions. Efforts to develop scalable, cost-effective production systems are crucial for equitable treatment availability.

Summary of Key Insights

- Intrathecal administration provides a safe, minimally invasive, and efficient route for targeted cell delivery.
- MSCs and NSCs remain the most promising therapeutic cell types, while exosome-based and gene-edited derivatives represent the next frontier.
- Optimal dosing appears to center around $1-2 \times 10^6$ cells/kg, though personalization is essential.
- Clinical improvements in motor and sensory function have been documented but remain moderate, highlighting the need for combination therapies and standardized clinical endpoints.
- Overcoming biological, ethical, and regulatory barriers will require coordinated, multidisciplinary research and international cooperation.

IV. FUTURE DIRECTIONS

The last decade has seen exponential growth in preclinical and clinical research exploring stem cell and cell-based therapies for spinal cord injury (SCI). Despite promising safety profiles and preliminary functional recovery, durable neurological restoration remains elusive. Future investigations must address the scientific, technical, and translational bottlenecks that currently impede clinical adoption.

4.1 Refinement of Cell Sources and Engineering

A major priority is the refinement of cell types to maximize regenerative efficacy while minimizing risks. The heterogeneity of mesenchymal stem cells (MSCs) across donors contributes to variability in therapeutic outcomes. Standardizing cell isolation, expansion, and characterization protocols is essential. Genetic engineering using **CRISPR/Cas9** or viral vectors can enhance trophic factor secretion, neuroprotective gene expression, and resistance to oxidative stress. Furthermore, combining different progenitor populations—such as MSCs with oligodendrocyte precursor cells (OPCs)—may synergize neuroprotective and remyelinating functions.

4.2 Optimization of Intrathecal Delivery Systems

While intrathecal administration offers a minimally invasive route, optimization of injection volume, rate, and distribution remains critical.

Advanced imaging and computational fluid dynamics can model cerebrospinal fluid (CSF) flow to predict cell dispersion and settling patterns. Future devices integrating **catheter-based micropumps** or **biodegradable carriers** may allow sustained, controlled release of cells or exosomes, enhancing retention and integration.

Hydrogel-based and **biomaterial scaffolds** have shown potential for improving local microenvironmental support. Biodegradable scaffolds composed of hyaluronic acid, collagen, or fibrin can be co-administered intrathecally to provide structural guidance and protect transplanted cells from shear stress. Integration of **nanotechnology**, such as magnetic nanoparticles, could further guide targeted localization of cells to lesion sites.

4.3 Dose Individualization and Personalized Regimens

A persistent challenge is defining the optimal therapeutic dose and frequency. Evidence suggests a non-linear dose-response curve, wherein excessive cell numbers may trigger immune activation or aggregation in the subarachnoid space. Personalized dosing algorithms incorporating patient weight, injury chronicity, and inflammatory markers could yield improved efficacy. **Machine learning-based predictive models** trained on large clinical datasets might eventually guide individualized treatment schedules.

Repeated intrathecal administrations—spaced at intervals tailored to cellular persistence—could maintain paracrine signaling and neuroprotection over prolonged periods. Longitudinal biomarker monitoring, including neurofilament light chain (NFL) and glial fibrillary acidic protein (GFAP) levels, can inform optimal retreatment timing.

4.4 Combining Cell Therapy with Adjunctive Modalities

True functional recovery likely requires **multimodal therapy** rather than monotherapy. Combining stem cell transplantation with **rehabilitation, electrical stimulation, neurotrophic factor administration, and immune modulation** may potentiate outcomes. Studies integrating **epidural stimulation** with intrathecal MSC delivery have demonstrated enhanced locomotor function compared with either intervention alone. Similarly, pharmacological priming with anti-inflammatory agents such as

minocycline may improve cell survival and engraftment.

4.5 Cell-Free and Exosome-Based Therapeutics

Cell-free approaches using exosomes or extracellular vesicles (EVs) are an emerging frontier. These nano-vesicles carry mRNAs, miRNAs, and proteins that replicate the paracrine effects of parent stem cells without immunogenicity or tumorigenic risk. Future research should focus on **standardizing exosome isolation**, determining effective dosing equivalents, and developing scalable production systems for clinical use. The potential to load exosomes with specific neuroprotective molecules or CRISPR components offers exciting prospects for **precision regenerative medicine**.

4.6 Clinical and Regulatory Outlook

To achieve clinical translation, harmonized regulatory frameworks are vital. Currently, the classification of stem cell products varies internationally, ranging from drugs to advanced therapy medicinal products (ATMPs). Regulatory convergence between agencies such as the **U.S. FDA, European Medicines Agency (EMA), and Indian Central Drugs Standard Control Organization (CDSCO)** will facilitate multinational trials and accelerate approvals.

Good Manufacturing Practice (GMP) compliance and validated potency assays must become mandatory for all clinical-grade cell preparations. Long-term post-marketing surveillance registries will be essential to monitor delayed adverse events. Furthermore, **ethical oversight** must ensure informed consent, equitable access, and transparency to prevent exploitation by unregulated stem-cell clinics.

4.7 Collaborative and Data-Driven Research Models

The field urgently needs **multicenter, randomized controlled trials** with standardized endpoints such as the ASIA score, electrophysiological indices, and imaging biomarkers. Shared data repositories and open-access registries can promote reproducibility and cross-validation. The adoption of **artificial intelligence (AI)** tools for pattern recognition in imaging and outcome prediction will strengthen the evidence base and identify patient subgroups most likely to benefit.

V. CONCLUSION

Intrathecal stem cell and cell-based therapies represent one of the most promising frontiers in spinal cord injury management. Over the past decade, preclinical and clinical studies have demonstrated that intrathecal delivery of MSCs, NSCs, and related derivatives can modulate the inflammatory milieu, promote angiogenesis, and stimulate limited neural regeneration. The procedure's minimally invasive nature and capacity for repeated dosing make it particularly suited for translation into clinical practice.

However, the path to widespread adoption remains complex. The field must address fundamental challenges including standardization of cell sources, dose optimization, manufacturing consistency, and long-term safety. Translational gaps between animal models and human pathology continue to hinder reproducibility. Moreover, ethical, regulatory, and economic factors will determine the scalability of these advanced therapies in real-world healthcare systems.

Future success will rely on **integrative strategies** that combine optimized cell formulations with supportive biomaterials, targeted rehabilitation, and precision monitoring. Interdisciplinary collaboration among neuroscientists, clinicians, bioengineers, and regulatory bodies is indispensable. As advances in cell engineering, biomaterials, and imaging converge, the vision of functional neural repair in SCI may transition from theoretical aspiration to clinical reality.

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