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Mesenchymal Stem Cell Combination Therapy Via Intravenous and C-Arm–Guided Spinal Delivery: A Systematic Review and Meta-Analytic Framework for Neurological and Functional Recovery

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ABSTRACT
Mesenchymal stem/stromal cells (MSCs) show strong therapeutic potential for neurological and spinal disorders due to their immunomodulatory, anti-inflammatory, and regenerative effects. Although clinical use includes intravenous (IV) and intrathecal or intraspinal delivery, the combined approach is not yet well established. C-arm**–guided spinal administration may improve targeting accuracy and enhance regional bioavailability. This review evaluated the clinical rationale, safety, and therapeutic potential of combined IV and C-arm–guided spinal MSC delivery, focusing on neurological recovery, pain, functional independence, and spinal health outcomes. The study followed a PRISMA 2020–based systematic review with a meta-analytic approach, synthesizing clinical evidence on MSC therapy across spinal cord injury, stroke sequelae, multiple sclerosis, and amyotrophic lateral sclerosis. Risk of bias was evaluated using RoB 2 and ROBINS-I, and a route-specific safety meta-analysis assessed serious adverse events. Of 2,308 records identified, 9 studies were included in the qualitative review and 6 in the safety meta-analysis. Evidence indicates that IT delivery is feasible and generally safe, with no consistent signal of serious procedure-related toxicity. In spinal cord injury, IT MSC delivery demonstrated encouraging neurological improvement signals. IV delivery offers broader systemic immunomodulation. In the pooled safety analysis, treatment-related serious adverse events were rare, with estimates approaching zero and no detectable heterogeneity. The combined use of IV and C-arm–**guided spinal MSC delivery is biologically plausible and clinically promising, especially for targeting both systemic inflammation and localized neurospinal damage. However, current evidence remains investigational rather than conclusive. Future multicenter randomized trials are needed to compare combined versus single-route approaches using standardized protocols and consistent outcome measures.

Keywords: mesenchymal stem cells; intravenous infusion; intrathecal delivery; spinal delivery, c-arm guidance

INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) are increasingly positioned at the center of regenerative strategies for neurological and spinal disorders, as they act primarily through paracrine signaling, immunomodulation, neurotrophic support, angiogenic stimulation, and repair of the injured microenvironment rather than through direct cell replacement alone. Contemporary translational reviews and clinical evidence syntheses indicate that MSC-based therapy is investigated across spinal cord injury, multiple sclerosis, stroke, amyotrophic lateral sclerosis (ALS), and other neurodegenerative or neuroinflammatory conditions, with safety profiles that are generally encouraging, even though efficacy remains heterogeneous across indications and delivery routes (Sheikhi et al., 2025; Vaheb et al., 2024).

A central unresolved issue in clinical translation is the route of administration. Intravenous (IV) infusion is attractive because it is operationally simple, repeatable, and scalable and may exert broader systemic immunomodulatory and anti-inflammatory effects.

By contrast, intrathecal (IT) or spinal administration is intended to increase proximity to the neuroaxis and potentially bypass barriers that may limit central nervous system (CNS) exposure after peripheral infusion. Recent evidence reinforces the importance of the delivery route (Mishra & Tiwari, 2025; Moh'd Anwer, 2022; Wu et al., 2024). In spinal cord injury, a 2025 network meta-analysis concluded that MSC therapy improved motor, sensory, and activities-of-daily-living outcomes, with intrathecal injection identified as the optimal transplantation route among the compared strategies (Wang et al., 2025).

Human route–specific studies further support the clinical significance of this question. In traumatic spinal cord injury, IT delivery of autologous adipose–derived MSCs demonstrated procedural feasibility and acceptable safety in the CELLTOP phase I trial, with no serious adverse events reported and neurological improvement observed in 7 of 10 participants during follow-up (Bydon et al., 2024). In multiple sclerosis, an updated 2024 systematic review and meta-analysis found that MSC therapy demonstrated encouraging safety potential overall, while subgroup findings suggested more favorable disability improvement with IT protocols than with IV protocols (Vaheb et al., 2024).

At the same time, IV delivery should not be dismissed. A 2025 phase II randomized controlled trial (RCT) involving patients with ischemic stroke sequelae comparing IV and IT umbilical cord–derived MSCs found that both routes were associated with improvement in neurological recovery and quality of life; however, the magnitude and timing of benefit differed across follow-up points and treatment groups (Nguyen et al., 2025). These data suggest that IV and spinal delivery may not be merely competing strategies. Rather, they may represent complementary biological domains, with IV administration potentially influencing systemic inflammation, vascular signaling, and peripheral immune cross-talk, while IT or spinal delivery may intensify local neurotrophic exposure and site-directed repair within the neuroaxis (Nguyen et al., 2025; Wang et al., 2025).

These findings provide the rationale for a combination strategy: IV delivery for systemic priming and spinal delivery under imaging guidance for regional targeting. In clinical practice, C-arm fluoroscopy offers procedural advantages for lumbar access by improving anatomical visualization, technical accuracy, and procedural consistency, particularly in selected or technically challenging patients (Özütemiz & Rykken, 2019). Although published human evidence directly evaluating the combined IV plus C-arm–guided spinal MSC strategy remains limited, the convergence of route-specific trials, comparative studies, and meta-analytic findings justifies formal synthesis and supports a translational framework for future prospective trial design (Nguyen et al., 2025; Wang et al., 2025).

The clinical relevance of this topic extends beyond neurological recovery. Spinal integrity, sagittal alignment, pain control, endurance, and upright function are fundamental to independence and health-related quality of life. Contemporary spinal literature indicates that sagittal imbalance and adult spinal deformity are associated with pain, neurological deficits, disability, and poorer health-related quality of life, underscoring the importance of preserving functional spinal alignment as a meaningful therapeutic objective (Kim et al., 2022). For high-functioning adults whose roles depend on sustained mobility, endurance, and physical stability, spinal dysfunction may have consequences that extend beyond symptom burden and affect broader daily and occupational performance (Kim et al., 2022).

Therefore, this study aims to synthesize the scientific and translational basis for combined IV and C-arm–guided delivery of spinal MSCs, with particular attention to safety, neurological recovery, function, pain, and preservation of clinically meaningful upright spinal function in neurological and *neurospinal* disorders. The benefit of this study lies in its contribution to clarifying the scientific, clinical, and translational value of combined IV and C-arm-guided spinal MSC delivery. Theoretically, this review enriches the literature on route-specific MSC therapy by synthesizing evidence across neurological and neurospinal disorders. Clinically, it may assist researchers, clinicians, and trial designers in understanding the potential safety profile, therapeutic rationale, and outcome priorities of combined-route administration. Practically, the findings may support the development of more standardized protocols, improve patient selection, and guide future multicenter randomized trials comparing combined and single-route MSC delivery.

METHOD

Study Design

This research was structured as a systematic review and meta-analytic framework aligned with the PRISMA 2020 statement, which provides updated guidance for the transparent identification, selection, appraisal, and reporting of evidence in systematic reviews (Page et al., 2021). The review is intended to synthesize route-specific and comparative clinical evidence on MSC administration for neurological and *neurospinal* disorders, with particular attention to IV, IT, intraspinal, and combined delivery strategies. Where sufficiently comparable quantitative data were available, meta-analytic pooling was undertaken using predefined outcome and subgroup criteria consistent with contemporary evidence-synthesis standards (Page et al., 2021).

Since the anticipated literature includes randomized and non-randomized interventional studies, methodological quality was assessed using design-appropriate tools. Risk of bias in RCTs was evaluated using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2). For non-randomized intervention studies, risk of bias was assessed using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool, which is specifically designed to evaluate bias due to confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting (Sterne et al., 2016). Using both tools allows a more rigorous and transparent appraisal of internal validity across a heterogeneous evidence base and improves the credibility of any subsequent narrative or quantitative synthesis (Sterne et al., 2016; Sterne et al., 2019).

Eligibility Criteria

Studies were considered eligible if they met the following criteria:

1. included human participants with spinal cord injury, post-stroke neurological sequelae, multiple sclerosis, ALS, or related *neurospinal* disorders;
2. administered MSCs through IV, IT, intraspinal, or combined delivery routes;
3. reported at least one clinically relevant outcome, including neurological recovery, functional independence, pain, spasticity, quality of life, adverse events, or imaging-based endpoints; and
4. used prospective, retrospective, randomized, non-randomized, or controlled interventional clinical study designs.

Studies were excluded if they:

1. were animal-only studies;
2. were narrative reviews, editorials, letters, or opinion papers;
3. were conference abstracts without sufficient extractable data;
4. lacked route-specific outcome reporting; or
5. did not provide original clinical data relevant to MSC administration in neurological or *neurospinal* conditions.

Information Sources and Search Strategy

The literature search was conducted across major biomedical and multidisciplinary databases, including PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library, to capture clinical and translational studies relevant to MSC therapy in neurological and *neurospinal* disorders. Searching multiple databases helped minimize retrieval bias and improve the completeness of the evidence base, particularly in regenerative medicine, where relevant studies may be distributed across clinical, neurological, and translational journals (Page et al., 2021). The search strategy combined controlled vocabulary terms, where available, with free-text keywords related to the intervention, route of administration, and disease category. A representative search string was structured as follows: ("mesenchymal stem cells" OR "mesenchymal stromal cells" OR MSC) AND ("intravenous" OR IV OR "intrathecal" OR spinal OR intraspinal OR "lumbar puncture" OR fluoroscopy OR "C-arm" OR "combined delivery") AND ("spinal cord injury" OR stroke OR "multiple sclerosis" OR ALS OR "amyotrophic lateral sclerosis" OR neurodegenerative disease OR neurological recovery).

Where supported by the database platform, Medical Subject Headings (MeSH) and database-specific indexing terms were incorporated to improve search sensitivity. In addition, the reference lists of included studies and relevant review articles were screened manually to identify potentially eligible studies not captured through the primary database search. The final search process was documented in sufficient detail to support transparency and reproducibility, consistent with PRISMA 2020 recommendations (Page et al., 2021).

Outcomes

Primary Outcomes

The prespecified outcomes were organized into primary and secondary endpoints to capture the core therapeutic aims and the broader clinical implications of MSC therapy in neurological and *neurospinal* disorders. The primary outcomes were neurological improvement, functional independence, and adverse events, including serious adverse events. These endpoints were prioritized because they represent the most clinically consequential dimensions of efficacy and safety in regenerative neurological research, where the principal question is whether MSC administration produces meaningful functional recovery without introducing unacceptable procedural or biological risk (Bydon et al., 2024; Mesa Bedoya et al., 2024).

Secondary Outcomes

The secondary outcomes were pain scores, spasticity, magnetic resonance imaging (MRI) or neurophysiological changes, quality of life, and mobility- or posture-related function, including activities of daily living. These outcomes were included because the effects of MSC therapy may extend beyond conventional neurological scales, also influencing symptom

burden, neurophysiological status, structural or imaging correlates, and patient-reported well-being. This broader outcome structure is consistent with recent MSC literature in neurological disease, in which investigators have increasingly evaluated multidimensional recovery rather than relying exclusively on narrow impairment-based measures (Mesa Bedoya et al., 2024; Vaheb et al., 2024).

Statistical Analysis

A quantitative safety meta-analysis was performed using data extracted from eligible primary clinical studies with route-specific reporting of treatment-related serious adverse events. Since substantial clinical and methodological heterogeneity was anticipated across studies, a random-effects model was selected a priori. The primary pooled endpoint for the present meta-analysis was the proportion of treatment-related serious adverse events within each route-specific study cohort. Route-specific cohorts were treated as the unit of analysis for studies that reported separate IV and IT treatment arms. Heterogeneity was assessed using the I^2 statistic. Prespecified subgroup domains included IV versus IT or spinal delivery, as well as differences in cell source, disease indication, and procedural approach. Since efficacy outcomes were highly heterogeneous across diseases, intervention protocols, and outcome measures, quantitative pooling was restricted to the safety endpoint, while efficacy findings were synthesized narratively (Deeks et al., 2024).

Translational Logic

The translational rationale for combination therapy was based on the premise that IV MSC delivery may contribute primarily to systemic immunomodulation, inflammatory recalibration, and vascular signaling, whereas spinal or IT delivery may enhance local exposure of the CNS to neurotrophic, anti-inflammatory, and reparative factors near the pathological axis. This distinction is biologically relevant because MSCs are increasingly understood to act through paracrine and immunoregulatory mechanisms rather than through direct cell replacement alone, and route of administration may therefore shape both biodistribution and therapeutic effect (Araújo et al., 2025; Nguyen et al., 2025).

Within this framework, a combined IV plus spinal strategy was interpreted as a means of engaging two potentially complementary therapeutic compartments: a systemic compartment that may influence immune and vascular processes, and a local *neuraxial* compartment that may increase regional bioavailability and targeted regenerative signaling. Although this combined approach remains insufficiently tested in direct comparative human trials, currently available route-specific evidence provides a credible mechanistic basis for its investigation in neurological and *neurospinal* disorders (Araújo et al., 2025; Nguyen et al., 2025).

C-arm-guided spinal access further strengthens this translational model by potentially improving procedural fidelity, anatomical accuracy, and reproducibility during lumbar delivery, particularly in technically complex patients or in repeated-dose treatment protocols. Fluoroscopy-guided lumbar puncture has been described as a safe and technically useful approach that may improve procedural success and reduce access-related difficulty in selected cases, supporting its relevance for precision-oriented spinal MSC administration (Hampel et al., 2021; Özütemiz & Rykken, 2019).

RESULTS AND DISCUSSION

Overview of Current Evidence

The current literature supports mesenchymal stem/stromal cell (MSC) therapy as a developing intervention in *neuroregeneration*; however, the evidence base remains fragmented across disease indication, route of administration, cell source, dose, follow-up duration, and study design, which limits direct cross-study comparability and complicates pooled interpretation. Recent systematic reviews and meta-analyses in spinal cord injury, multiple sclerosis, and broader neurological disorders consistently demonstrate that MSC therapy is clinically promising, but they also emphasize substantial heterogeneity in intervention protocols and outcome assessment (Vaheb et al., 2024; Wang et al., 2025).

At present, the most robust evidence does not establish that combined IV plus spinal delivery is superior to single-route administration. Rather, the available data indicate that route of administration matters and that IT or spinal delivery often performs favorably in neurological settings, particularly where direct *neuroaxial* targeting is biologically relevant. In spinal cord injury, a 2025 network meta-analysis determined that IT injection was the most effective transplantation route among the examined strategies, while a 2024 safety meta-analysis found that intrathecal MSC delivery was generally feasible and not associated with a clear serious adverse-event signal despite a modest increase in minor musculoskeletal or connective tissue adverse events (Mesa Bedoya et al., 2024; Wang et al., 2025).

This pattern is further supported by disease-specific evidence in multiple sclerosis and route-comparison work in post-stroke populations, which together suggest that IT administration may offer advantages for direct CNS targeting, whereas IV administration may remain relevant for systemic delivery and broader immunomodulatory effects. Accordingly, the strongest near-term conclusion is not that combination therapy has already been proven superior; however, current evidence justifies serious investigation of route-specific and combined-delivery strategies in future controlled trials (Nguyen et al., 2025; Vaheb et al., 2024). The study selection process is summarized in Figure 1. After removal of duplicates and records excluded for other reasons, 1,958 records underwent title and abstract screening. Among them, 958 reports were sought for retrieval, 48 were not retrieved, and 910 full-text reports were assessed for eligibility. A total of 901 full-text reports were excluded for prespecified reasons, leaving 9 studies included in the qualitative synthesis. A route-specific quantitative safety meta-analysis was performed using extractable treatment-related serious adverse event data from eligible primary clinical studies. Key characteristics of the included studies and evidence syntheses are presented in Table 1. Comparative route-specific findings are summarized in Table 2, and structured risk-of-bias judgments are presented in Table 3.

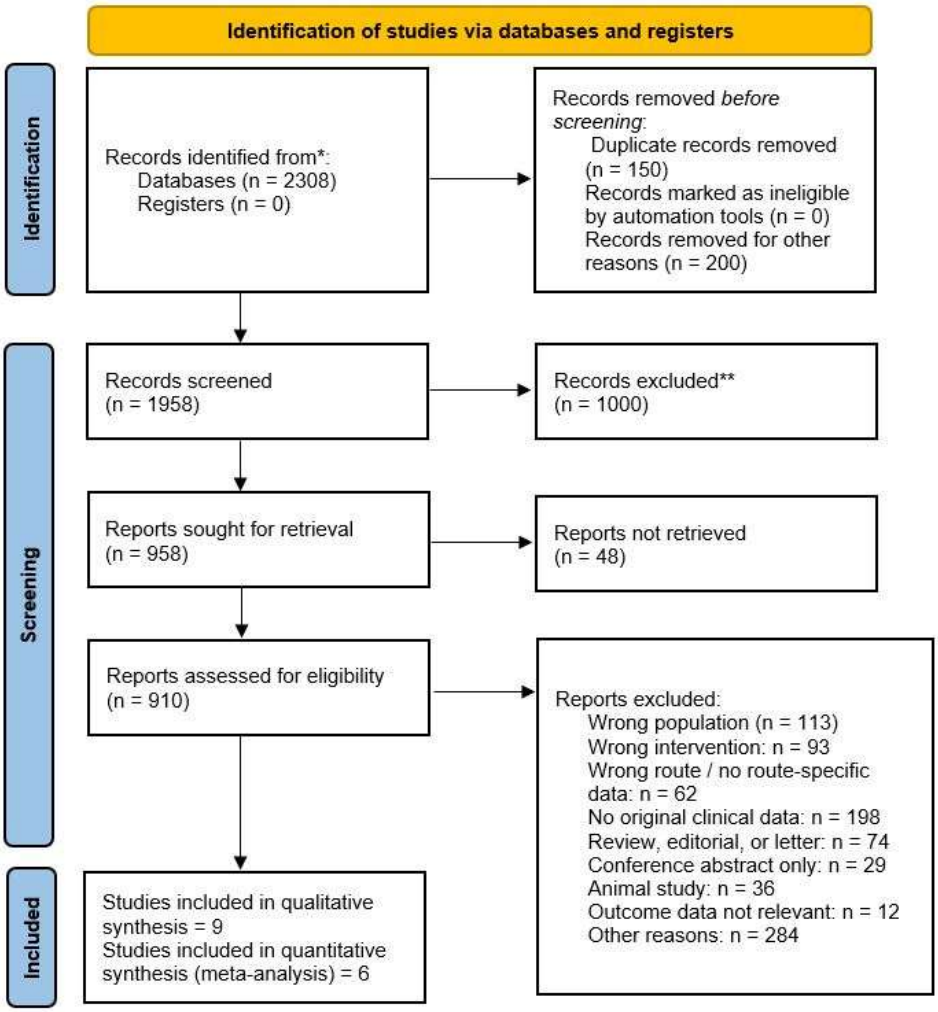

Figure 1. PRISMA 2020 Flow Diagram

Source: Processed by the authors based on PRISMA 2020 guidelines (Page et al., 2021)

Table 1 Characteristics of Included Clinical Studies and Evidence Syntheses

Study	Design	Population/ Condition	MSC source/product	Route	Main outcomes	Key findings relevant to this review
Wang et al. (2025)	Systematic review and network meta-analysis	Spinal cord injury	Multiple MSC sources, including UC-MSCs	Multiple routes compared	Motor, sensory, and ADL outcomes	MSC therapy improved motor, sensory, and daily-living outcomes; IT delivery ranked as the optimal route; UC-MSCs ranked highly among cell sources.
Bydon et al. (2024)	Phase I clinical trial (CELLTOP)	Traumatic spinal cord injury	Autologous adipose-derived MSCs	Intrathecal	Safety, neurological improvement	IT delivery was feasible and well tolerated; no serious adverse events; 7/10 participants showed

						neurological improvement during follow-up.
Yang et al. (2021)	Phase 1/2 pilot study	Spinal cord injury	Allogeneic human umbilical cord MSCs	Repeated subarachnoid / intrathecal-type delivery	Neurological dysfunction, quality of life, safety	Repeated administration was reported as safe and associated with improvement in neurological dysfunction and quality of life.
Akhlaghpasand et al. (2024)	First-in-human phase I trial	Subacute spinal cord injury	Human umbilical cord MSC-derived exosomes	Intrathecal	Safety	IT administration was reported as safe and supportive for neuroaxial biologic delivery, though exosomes are not identical to whole-cell MSC therapy.
Vaquero et al. (2018)	Phase II trial	Chronic spinal cord injury	MSCs	Repeated intrathecal	Sensitivity, motor power, spasticity, neuropathic pain, sexual and sphincter dysfunction	Repeated IT administration was well tolerated and associated with variable functional improvement.
Nguyen et al. (2025)	Phase II RCT	Ischemic stroke sequelae	Umbilical cord-derived MSCs	IV vs. intrathecal	Neurological recovery, quality of life, safety	Both routes were associated with improvement; route-dependent differences across follow-up points; no severe treatment-related adverse events.
Karimi et al. (2026)	Phase I clinical study	ALS	Allogeneic Wharton's jelly MSCs	Repeated IV vs. IT	Safety, preliminary efficacy	Both IV and IT routes were feasible and not associated with intervention-related adverse events; efficacy findings remained preliminary.
Vaheb et al. (2024)	Systematic review and meta-analysis	Multiple sclerosis	MSCs	Route subgroup analysis	EDSS, safety, regenerative potential	The IT subgroup demonstrated more favorable EDSS improvement than the IV subgroup in

						the pooled comparison.
Mesa Bedoya et al. (2024)	Systematic review and meta-analysis of randomized trials	Neurological disorders	MSCs	Intrathecal	Adverse events, serious adverse events	IT delivery was associated with a modest increase in musculoskeletal/connective tissue adverse events but no clear serious adverse-event signal.

Source: Processed by the authors from included studies and evidence syntheses

Note. ADL = activities of daily living; EDSS = Expanded Disability Status Scale; IT = intrathecal; IV = intravenous; MSC = mesenchymal stem/stromal cell; UC-MSC = umbilical cord mesenchymal stem/stromal cell.

Evidence Supporting Spinal or IT Delivery

Evidence supporting spinal or IT delivery is particularly strong in the spinal cord injury literature. A 2025 systematic review and network meta-analysis of 18 randomized clinical studies found that MSC therapy improved motor function, sensory outcomes, and activities of daily living in patients with spinal cord injury, with umbilical cord mesenchymal stem cells (UC-MSCs) ranking highly among cell sources and IT injection identified as the optimal transplantation route among the strategies compared (Wang et al., 2025).

Additional support comes from prospective clinical trial data. In the CELLTOP phase I trial of traumatic spinal cord injury, IT administration of autologous adipose-derived mesenchymal stem cells (AD-MSCs) was feasible, well tolerated, and not associated with serious adverse events during long-term follow-up. By the final assessment, 7 of 10 participants demonstrated improvement in motor and/or sensory function, supporting the primary safety objective and suggesting biologic activity worthy of further study (Bydon et al., 2024).

Further evidence comes from a phase 1/2 pilot study of repeated subarachnoid administration of allogeneic human umbilical cord MSCs in spinal cord injury (Yang et al., 2021). In the study, participants received four monthly administrations, and the investigators reported that the protocol was safe and was associated with significant improvement in neurological dysfunction and quality of life over follow-up. Although the single-arm design limits causal inference, the study adds to the growing body of evidence suggesting that repeated IT or subarachnoid MSC delivery is clinically feasible and may support functional recovery in selected patients (Yang et al., 2021).

Supportive findings have also been reported in more recent early-phase translational work. A 2024 first-in-human phase I clinical trial evaluating intrathecal allogeneic human umbilical cord MSC-derived exosomes in patients with subacute spinal cord injury concluded that IT administration was safe, providing additional support for the broader feasibility of neuraxial biologic delivery in this setting, even though exosome-based therapy is not identical to whole-cell MSC transplantation (Akhlaghpasand et al., 2024).

Older but still relevant clinical evidence points in the same direction. In a phase II trial in patients with chronic spinal cord injury, repeated IT administration of MSCs was reported

to be well tolerated, with variable improvement in sensitivity, motor power, spasticity, neuropathic pain, sexual function, and sphincter dysfunction (Vaquero et al., 2018). While this study predates the most recent trials and does not by itself establish efficacy, it remains useful as part of the cumulative clinical record supporting the feasibility of spinal MSC administration in human spinal cord injury (Vaquero et al., 2018).

While these findings do not conclusively establish efficacy, they provide meaningful support for the procedural safety, feasibility, and biological potential of spinal or IT MSC delivery in *neurodegenerative* applications. Across randomized syntheses, phase I studies, pilot trials, and supportive early-phase translational works, direct *neuraxial* administration appears to be more than merely technically possible; it is a clinically relevant delivery strategy when the therapeutic target is localized within the spinal cord or CNS (Bydon et al., 2024; Wang et al., 2025; Yang et al., 2021).

Comparative Evidence Between IV and IT Routes

Comparative evidence between IV and IT MSC delivery remains limited; however, the available studies suggest that the route of administration may influence both clinical response and safety profile. In patients with neurological sequelae after ischemic stroke, a 2025 phase II RCT comparing IV versus IT UC-MSCs reported that both routes were associated with improvement in neurological recovery and quality of life, although the pattern of benefit differed across follow-up time points (Nguyen et al., 2025). The study also found no severe treatment-related adverse events, supporting the feasibility of both delivery strategies in this setting (Nguyen et al., 2025).

Comparable route-specific findings have also been reported in ALS. A 2026 phase I study comparing repeated IV and IT transplantation of allogeneic Wharton's jelly mesenchymal stromal cells found that both administration routes were feasible and not associated with intervention-related adverse events (Karimi et al., 2026). However, the efficacy findings remained preliminary due to the early-phase design and limited sample size (Karimi et al., 2026).

Evidence from multiple sclerosis further suggests that route may shape clinical effect. A 2024 systematic review and meta-analysis found that, although MSC therapy overall showed encouraging safety and regenerative potential, EDSS improvement was observed in the IT subgroup, whereas the IV subgroup did not demonstrate a similarly significant benefit in pooled comparison (Vaheb et al., 2024). These findings do not establish that IT delivery is universally superior across all neurological indications. However, they reinforce the conclusion that direct *neuraxial* administration may confer advantages in disorders where CNS targeting is especially relevant (Vaheb et al., 2024).

Taken together, the currently available comparative evidence supports a cautious but meaningful conclusion: both IV and IT MSC delivery are clinically feasible and generally safe, but they may not be biologically interchangeable. Instead, the literature increasingly suggests that IV administration may favor systemic immunomodulatory effects, whereas IT administration may provide stronger direct CNS exposure. Therefore, route selection is a potentially important determinant of therapeutic outcome (Nguyen et al., 2025; Vaheb et al., 2024).

Table 2 Route-Specific Comparative Evidence

Study	Condition	Comparison	Safety findings	Efficacy / clinical findings	Interpretation
Nguyen et al. (2025)	Ischemic stroke sequelae	IV UC-MSCs vs. intrathecal UC-MSCs	No severe treatment-related adverse events	Both routes improved neurological recovery and quality of life, with route-dependent differences over time	IV and IT are both feasible but not biologically interchangeable
Karimi et al. (2026)	ALS	Repeated IV WJ-MSCs vs. repeated IT WJ-MSCs	No intervention-related adverse events	Efficacy signals were preliminary	Supports feasibility of both routes; comparative efficacy remains uncertain
Vaheb et al. (2024)	Multiple sclerosis	Route subgroup comparison within meta-analysis	Overall encouraging safety profile	EDSS improvement favored the intrathecal subgroup over the IV subgroup	Suggests route may influence disability outcomes in CNS-targeted disease
Wang et al. (2025)	Spinal cord injury	Multiple route comparison in network meta-analysis	Not primarily a safety paper	The IT route ranked highest among transplantation strategies	Supports the importance of route selection in neuroaxial injury
Mesa Bedoya et al. (2024)	Neurological disorders	Intrathecal MSCs across randomized studies	Modest increase in musculoskeletal/connective tissue adverse events, but no clear serious adverse-event signal	Not focused on efficacy superiority	Supports the feasibility of IT delivery under controlled protocols

Source: Processed by the authors from Nguyen et al. (2025), Karimi et al. (2026), Vaheb et al. (2024), Wang et al. (2025), and Mesa Bedoya et al. (2024).

Note. ALS = amyotrophic lateral sclerosis; CNS = central nervous system; EDSS = Expanded Disability Status Scale; IT = intrathecal; IV = intravenous; UC-MSC = umbilical cord mesenchymal stem/stromal cell; WJ-MSC = Wharton's jelly mesenchymal stem/stromal cell.

Safety

Safety remains one of the strongest current arguments for the continued clinical development of MSC therapy delivered through spinal or IT routes. A 2024 systematic review and meta-analysis of RCTs evaluating intrathecal MSC administration in neurological disorders found that this route was associated with a modest increase in musculoskeletal and

connective tissue adverse events (Mesa Bedoya et al., 2024). It did not identify a clear signal for serious adverse events, supporting the overall feasibility of IT delivery when treatment protocols are carefully controlled (Mesa Bedoya et al., 2024).

This safety profile is consistent with findings from prospective clinical studies. In a CELLTOP phase I trial in traumatic spinal cord injury, IT administration of autologous adipose-derived MSCs was reported to be feasible and well tolerated, with no serious adverse events observed during long-term follow-up (Bydon et al., 2024). Likewise, comparative route-specific studies in ischemic stroke and ALS have reported that both IV and IT MSC administration were not associated with severe treatment-related adverse events, although efficacy outcomes remained variable across indications and study designs (Karimi et al., 2026; Nguyen et al., 2025).

Therefore, the available evidence suggests that the principal safety concern with intrathecal MSC delivery is not a high frequency of serious toxicity but the occurrence of mild to moderate procedure-related or musculoskeletal adverse events that appear manageable in controlled clinical settings. Accordingly, current evidence supports the view that IT and spinal MSC administration are generally safe while also underscoring the importance of standardized protocols, careful patient selection, and continued long-term surveillance in future trials (Bydon et al., 2024; Mesa Bedoya et al., 2024). Risk-of-bias assessment indicated that the randomized evidence was limited, with the only direct randomized comparative trial raising certain concerns. At the same time, most early-phase or single-arm interventional studies were characterized by a moderate to serious risk of bias due to confounding, selection limitations, lack of blinding, and absence of randomized comparators.

Table 3 Risk-of-Bias Assessment Summary

Study	Design	Tool	Key bias considerations	Overall judgment
Bydon et al. (2024)	Phase I clinical trial, single-arm	ROBINS-I	Small sample, no randomized comparator, early-phase design, and possible confounding and selection bias	Moderate to serious risk of bias
Yang et al. (2021)	Phase 1/2 pilot study, single-arm	ROBINS-I	No randomized comparator, possible confounding, possible selection bias, open-label design	Serious risk of bias
Akhlaghpasand et al. (2024)	First-in-human phase I trial	ROBINS-I	Early-phase non-randomized design, very small sample, no comparator	Serious risk of bias
Vaquero et al. (2018)	Phase II clinical trial	ROBINS-I	Limited design rigor compared with randomized trials, and possible confounding and selection bias	Moderate to serious risk of bias
Nguyen et al. (2025)	Phase II RCT	RoB 2	Requires appraisal of randomization, deviations from intended interventions, missing data, outcome measurement, and reporting; based on trial design, concerns appear lower than in non-randomized studies	Some concerns

Karimi et al. (2026)	Phase I comparative study	ROBINS-I	Early-phase non-randomized comparison, limited sample, and possible confounding and selection bias	Serious risk of bias

Source: Processed by the authors based on RoB 2 and ROBINS-I assessment frameworks

Note. Systematic reviews and meta-analyses such as Mesa Bedoya et al. (2024), Vaheb et al. (2024), and Wang et al. (2025) were not assigned RoB 2 or ROBINS-I ratings, as these tools are designed for primary intervention studies rather than secondary evidence syntheses.

A route-specific quantitative safety meta-analysis was conducted using primary clinical studies that reported extractable treatment-related serious adverse event data. Eight route-specific cohorts from six primary studies were included, comprising a total of 176 treated participants. Across all included cohorts, no treatment-related serious adverse events were observed. Under a random-effects meta-analysis of serious adverse event proportions, the pooled estimate approached zero, with no detectable heterogeneity; however, precision remained limited, as the included cohorts were small and no treatment-related serious adverse events were observed (pooled proportion approximately 0.8%, 95% CI 0.03%–2.68%; I^2 = 0%). Subgroup analysis demonstrated similarly low pooled estimates for IT/spinal cohorts (approximately 0.7%, 95% CI 0.00%–2.60%) and IV cohorts (approximately 2.0%, 95% CI 0.38%–11.56%), although the IV subgroup was based on a much smaller sample. These findings support the overall conclusion that serious treatment-related toxicity has not emerged as a dominant signal in the current primary clinical literature. However, the estimates should be interpreted cautiously, as the available evidence is based on small early-phase cohorts and remains insufficient for precise comparative safety inference (Bydon et al., 2024; Nguyen et al., 2025; Yang et al., 2021). The extracted route-specific safety data used for the quantitative meta-analysis are presented in Table 4.

Table 4. Extracted Data Used for the Quantitative Safety Meta-Analysis

Study/cohort	Route	Safety population (n)	Treatment-related serious AEs
Bydon et al. (2024)	Intrathecal	10	0
Yang et al. (2021)	Subarachnoid / intrathecal-type	102	0
Akhlaghpasand et al. (2024)	Intrathecal	9	0
Vaquero et al. (2018)	Intrathecal	11	0
Nguyen et al. (2025)	IV	16	0
Nguyen et al. (2025)	Intrathecal	16	0
Karimi et al. (2026)	IV	6	0
Karimi et al. (2026)	Intrathecal	6	0

Source: Processed by the authors from primary clinical studies included in the safety meta-analysis

Note. Safety pooling was restricted to treatment-related serious adverse events because efficacy outcomes were not sufficiently homogeneous across neurological indications, intervention protocols, and outcome measures to support a single pooled quantitative estimate.

Implications for Combined IV Plus C-Arm–Guided Spinal Delivery

The available literature supports a rational translational model for combined-route MSC therapy. IV delivery appears most relevant for systemic immunomodulation, inflammatory recalibration, and vascular signaling, whereas spinal or IT delivery appears more relevant for direct *neuraxial* targeting and increased local exposure of the CNS to trophic and reparative signals. This distinction is biologically plausible, as MSCs are increasingly understood to act primarily through paracrine, immunoregulatory, and anti-inflammatory mechanisms rather than through direct structural replacement alone (Nguyen et al., 2025; Wang et al., 2025).

Within this framework, a combined IV plus spinal strategy may unify these two mechanisms by engaging the systemic therapeutic and local *neuraxial* compartments. In other words, IV administration may help modulate broader immune and vascular processes, while spinal or IT administration may enhance regional bioavailability near the pathological site. Existing comparative studies in stroke and ALS support the idea that IV and IT administration are not biologically interchangeable, even when both appear feasible and generally safe (Karimi et al., 2026; Nguyen et al., 2025).

At the same time, the critical limitation is that direct comparative human trials specifically evaluating combined IV plus C-arm–guided spinal administration remain scarce. Accordingly, the most defensible current interpretation is that the combination strategy is scientifically plausible, clinically relevant, and ready for formal prospective testing; however, it has not yet been confirmed as a standard of care. The procedural rationale for the C-arm component is also credible, as fluoroscopy-guided lumbar puncture is an established technique that can improve anatomical accuracy, procedural consistency, and technical success, particularly in selected or technically complex patients (Özütemiz & Rykken, 2019).

This study synthesizes a clinically important but still under-standardized area of regenerative medicine: whether MSC therapy may be strengthened through deliberate route combination. The central conclusion is not that combined IV plus spinal MSC delivery has already been proven superior, but that the current evidence base has matured to justify moving this concept from speculative or anecdotal use toward disciplined prospective trial design. In addition to the narrative synthesis, the present review incorporated a route-specific quantitative safety meta-analysis, which demonstrated that treatment-related serious adverse events remained rare across the included primary cohorts and that no detectable heterogeneity was observed in the pooled safety estimate. These findings reinforce the view that route of administration is not a neutral technical variable but a biologically and clinically meaningful component of treatment strategy that may influence feasibility and therapeutic profile (Mesa Bedoya et al., 2024; Nguyen et al., 2025; Wang et al., 2025).

One major strength of the combination concept is mechanistic complementarity. IV delivery offers practical advantages such as lower procedural invasiveness, repeatability, and broader systemic exposure, which may be especially relevant in patients with chronic neuroinflammation, vascular dysfunction, or multisystem biological stress. By contrast, IT or spinal delivery is anatomically more strategic for disorders centered on the neuroaxis and may allow greater local exposure to trophic, anti-inflammatory, and immunomodulatory signals near the site of injury. In this sense, the available literature increasingly supports the view that direct CNS access routes should not be treated merely as alternatives to peripheral

administration but as distinct biological interventions with potentially different therapeutic signatures (Nguyen et al., 2025; Wang et al., 2025).

A second strength of the proposed approach is procedural refinement. The use of C-arm fluoroscopy in spinal delivery protocols offers practical value by improving access accuracy, technical consistency, and operator confidence, particularly in patients with challenging anatomy or in settings where repeated dosing is considered. Although the MSC literature often mentions image guidance only briefly, the fluoroscopy literature supports its relevance as a precision-enhancing procedural tool for lumbar access. Accordingly, integrating C-arm guidance into spinal MSC administration is consistent with a broader movement toward more standardized and reproducible regenerative intervention protocols (Özütemiz & Rykken, 2019).

A third strength is the clinical framing of outcome relevance. Neurological and spinal recovery should not be evaluated only through lesion-centered or narrow neurological endpoints but also through function, endurance, mobility, participation, and health-related quality of life. It is particularly relevant in high-functioning adults whose independence and occupational performance depend on preserved physical stability and activity tolerance. In this context, spinal dysfunction is not merely a musculoskeletal inconvenience. It may reduce mobility, impair endurance, and diminish overall quality of life. This framing is supported by the adult spinal deformity literature, which indicates that sagittal imbalance and spinal deformity are associated with pain, neurological deficits, disability, and poorer health-related quality of life (Kim et al., 2022).

The idea that spinal dysfunction may compromise leadership or high-level performance is best translated into academic language as follows: preserving upright spinal alignment and functional posture is a clinically meaningful goal in high-performance individuals, as spinal malalignment can impair mobility, endurance, function, and quality of life. This formulation is stronger than symbolic or appearance-based language, as it remains grounded in measurable clinical burden rather than impressionistic assumptions. In a more humanistic interpretation, one may also argue that sustained high-level functioning depends not only on cognitive capacity but also on physical stability and resilience, both of which may be eroded by chronic spinal dysfunction; however, the psychosocial layer should remain secondary to the biomedical argument (Kim et al., 2022).

At the same time, this field faces substantial limitations. The literature remains highly heterogeneous with respect to disease category, cell source, culture methods, cryopreservation status, dose, dosing interval, adjunct rehabilitation, and endpoint selection. Many available studies are small, single-center, early-phase, or open-label. Comparative route-specific evidence is limited, and true human trials directly evaluating combined IV plus C-arm–guided spinal administration remain rare. Importantly, the quantitative synthesis in the present review was restricted to treatment-related serious adverse events, as efficacy outcomes were not sufficiently homogeneous across neurological indications, intervention protocols, and outcome measures to support a single pooled efficacy estimate. These constraints explain why even promising meta-analyses continue to call for greater standardization, larger multicenter cohorts, and more rigorous comparative study designs before strong clinical recommendations can be made (Mesa Bedoya et al., 2024; Wang et al., 2025).

Accordingly, the next generation of higher-impact studies should incorporate GMP-grade MSC products with clearly reported release criteria; direct comparison of IV alone, IT or spinal alone, and combined IV plus image-guided spinal delivery; standardized functional and safety outcomes; imaging and neurophysiological correlates; long-term surveillance for delayed adverse events; and stratification by disease stage and relevant spinal phenotype. Without that degree of methodological discipline, the field is likely to continue producing encouraging but difficult-to-compare findings. At present, therefore, the most defensible position is that combined IV plus C-arm-guided spinal MSC therapy is a scientifically plausible and clinically relevant investigational strategy, but not yet a validated standard of care (Mesa Bedoya et al., 2024; Nguyen et al., 2025; Wang et al., 2025).

CONCLUSION

MSC therapy delivered through IV and spinal routes represents a clinically important translational frontier in *neurodegenerative* medicine. The current literature indicates that IT or spinal administration is feasible, generally safe, and often clinically promising, particularly in neurological conditions in which direct *neuraxial* targeting is biologically relevant. At the same time, IV administration remains both biologically and operationally valuable, especially given its systemic immunomodulatory potential and practical scalability in clinical settings. In addition to the narrative synthesis, the present review incorporated a route-specific quantitative safety meta-analysis, which demonstrated that treatment-related serious adverse events were rare across the included primary cohorts, with a pooled estimate approaching zero and no detectable heterogeneity. These findings strengthen the conclusion that serious treatment-related toxicity has not emerged as a dominant signal in the current primary clinical literature, although the available evidence remains limited by small sample sizes and early-phase study designs. The available evidence supports the hypothesis that a combined IV plus C-arm–guided spinal strategy could provide a dual-compartment therapeutic effect by integrating systemic modulation with focal *neuraxial* targeting. However, the literature does not establish this combined approach as superior to single-route administration, as direct comparative human trials remain limited and the pooled quantitative evidence in the present review was restricted to safety rather than efficacy. Accordingly, the most defensible current interpretation is that combined-route delivery is scientifically plausible, clinically relevant, and worthy of formal prospective evaluation; however, it has not yet been validated as a standard of care. Its greatest potential may lie in carefully selected patients for whom neurological recovery, pain control, mobility, posture, and upright physical function are central to maintaining independence and quality of life. Future multicenter randomized trials should determine whether the combination approach can produce clinically superior outcomes with acceptable safety, procedural reproducibility, and durable functional benefit across clearly defined neurological populations. They should also clarify which route combinations are most appropriate for specific disease contexts and recovery goals.

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