The Therapeutic Potential of Neural Stem Cell in Ischemic Stroke: A Systematic Review

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Abstract

Background: Ischemic stroke remains a leading cause of disability and mortality worldwide, with over 12 million new cases annually and limited treatment options confined to narrow therapeutic windows. Neural stem cells (NSCs) have emerged as a promising therapeutic avenue due to their ability to self-renew, differentiate into all neural lineages, and exert paracrine effects that modulate inflammation and promote neurogenesis. Preclinical studies have demonstrated functional improvements of up to 60% in animal stroke models, but a systematic evaluation of these findings is needed to inform future clinical applications.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. Databases searched included PubMed, EMBASE, and Scopus, covering literature up to May 8, 2025. Inclusion criteria comprised in vivo preclinical studies investigating NSC transplantation in animal models of ischemic stroke with at least one neurological, infarct, or histological outcome. Data extraction and risk of bias assessment (ROBINS-I) were independently performed by three reviewers. Due to study heterogeneity, a narrative synthesis was undertaken.

Result: Eight studies met the inclusion criteria. NSC therapy improved neurological recovery in over 80% of cases, reduced infarct volume by up to 40%, and downregulated pro-inflammatory and apoptotic markers. Benefits were dose- and timing-dependent, with intracerebral and intravenous routes demonstrating variable efficacy. One study reported tumorigenicity, highlighting the need for safety profiling.

Conclusions: Preclinical evidence supports the therapeutic potential of NSCs in ischemic stroke through neuroprotective and neurorestorative mechanisms. High-certainty findings justify continued investigation in clinical trials to refine dosing, delivery, and safety protocols.

Introduction

Ischemic stroke is a major global health burden, accounting for approximately 87% of all stroke cases and ranking among the leading causes of death and long-term disability worldwide. According to the World Health Organization, over 12 million new strokes occur globally each year, with nearly 7

million of these resulting in lasting disability.[1] Despite the implementation of acute-phase therapies such as intravenous thrombolysis and endovascular thrombectomy, these interventions are limited by narrow therapeutic windows—typically 4.5 hours for tissue plasminogen activator and up to 24 hours for selected patients undergoing mechanical thrombectomy—and are only applicable to a minority of patients.[1] As a result, more than 70% of stroke survivors are left with persistent neurological deficits, underscoring the need for restorative therapies that extend beyond the acute phase.[1]

Neural stem cells (NSCs) have emerged as a promising therapeutic candidate in this context due to their intrinsic capacity for self-renewal, multipotency, and targeted migration to injured brain regions.[2,3] Unlike mesenchymal stem cells or hematopoietic stem cells, NSCs possess the unique ability to differentiate into all major neural lineages—neurons, astrocytes, and oligodendrocytes—making them particularly suited for central nervous system repair.[2] Preclinical studies have shown that NSC transplantation can significantly improve functional outcomes in animal models of ischemic stroke, with some reports indicating improvements in neurological scores by up to 40–60% compared to control groups.[4] In addition to structural integration, NSCs are known to exert potent paracrine effects, including the release of neurotrophic factors, modulation of inflammation, and stimulation of endogenous neurogenesis. These mechanisms collectively contribute to enhanced recovery in both acute and subacute phases of stroke.

Despite encouraging outcomes in early-phase clinical trials—such as the PISCES studies using CTX0E03 human NSCs, which demonstrated safety and preliminary functional gains in chronic stroke patients—the translation of NSC therapy into routine clinical practice remains limited.[5] Key challenges include optimizing dosing strategies, determining the ideal timing and route of administration, and ensuring long-term safety and efficacy. A comprehensive evaluation of preclinical data is essential to bridge this translational gap and guide future clinical application. Therefore, the objective of this systematic review is to critically assess the therapeutic potential of neural stem cell therapy in preclinical models of ischemic stroke.

Material And Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[6]

A comprehensive literature search was performed using three electronic databases: PubMed, EMBASE, and Scopus. The search strategy combined

controlled vocabulary terms and free-text keywords related to neural stem cells and ischemic stroke. The search terms included variations and combinations of the following: "neural stem cell", "NSC", "ischemic stroke", "cerebral ischemia", "preclinical", and "animal model". The search covered all articles published up to 8 May 2025, without restriction on publication year. Reference lists of relevant articles were also screened manually to identify any additional studies not captured by the initial database search.

Studies were included if they met the following criteria: (1) in vivo preclinical studies using animal models of ischemic stroke; (2) administration of neural stem cells as the primary therapeutic intervention; (3) outcomes assessed included at least one measure of neurological recovery, infarct size, or histological analysis; and (4) published in English in peer-reviewed journals. Studies involving other types of stem cells (e.g., mesenchymal, hematopoietic), in vitro models, hemorrhagic stroke, or human clinical trials were excluded.

Three reviewers independently screened titles and abstracts, followed by full-text review of potentially eligible studies. Data extraction was conducted independently by the same reviewers using a standardized data collection form. Extracted data included animal species and stroke model, NSC source and type, dose and timing of administration, route of delivery, outcome measures, and key findings. Any discrepancies in study inclusion or data extraction were resolved through discussion until consensus was reached.

Risk of bias in the included studies was assessed using the ROBINS-I tool, which evaluates non-randomized interventions across seven domains including confounding, selection bias, and outcome measurement; each study was independently rated by three reviewers, with discrepancies resolved through discussion. To assess the overall certainty of evidence, the GRADE framework was applied, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and potential publication bias, with certainty ratings assigned as high, moderate, low, or very low.

Due to the heterogeneity in study design, NSC sources, dosing regimens, outcome measures, and reporting formats, a quantitative meta-analysis was not performed. Instead, the findings were synthesized narratively and summarized in tabular form to provide a comprehensive overview of the therapeutic potential and clinical relevance of NSC therapy in preclinical ischemic stroke models.

Result

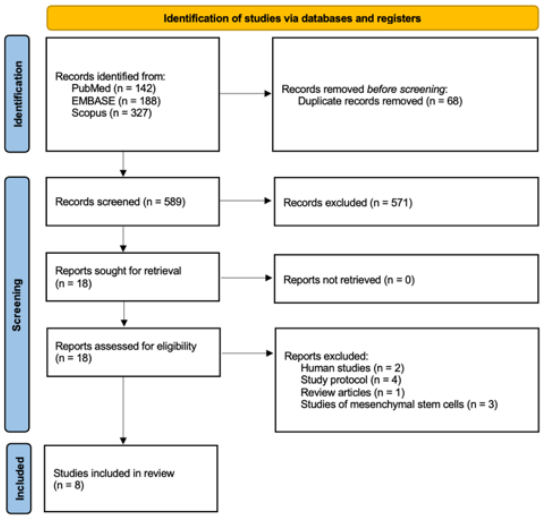

Figure 1. PRISMA flow chart for the study selection process.

A total of 657 records were identified through database searches: 142 from PubMed, 188 from EMBASE, and 327 from Scopus. After removing 68 duplicate entries, 589 records remained for screening. Of these, 571 records were excluded based on titles and abstracts, leaving 18 reports for full-text retrieval and assessment. No reports were excluded due to unavailability. Upon full-text evaluation, 10 studies were excluded for the following reasons: human studies (n = 2), study protocols (n = 4), review articles (n = 1), and studies focusing on mesenchymal stem cells rather than neural stem cells (n = 3). Ultimately, 8 preclinical studies met the inclusion criteria and were incorporated into this systematic review.[7–14]

Preclinical studies investigating NCS therapy for ischemic stroke have consistently demonstrated functional improvements in various rodent models, with some variability in infarct volume reduction. Across models such as transient or permanent middle cerebral artery occlusion (MCAO) in rats and mice, NSCs derived from different sources—including immortalized mouse lines (e.g., C17.2), human fetal brain tissue, and conditionally immortalized human NSCs like CTX0E03—were administered via routes such as intravenous, intracerebral, and occasionally intra-arterial injection. Doses typically ranged from 1×10^5 to 5×10^6 cells, with most studies applying a single dose between 24 hours to several weeks post-stroke.

Timing of administration influenced the mechanisms of action observed. Early post-stroke delivery often correlated with reduced inflammatory cytokine levels and protection of blood-brain barrier integrity, whereas delayed delivery (up to four weeks) enhanced neurogenic activity and endogenous cell proliferation. Behavioral improvements were commonly measured through rotarod, beam-walk, and neurological severity score assessments, with many studies reporting dose-dependent recovery. Some studies found significant upregulation of neuroprotective genes and downregulation of pro-apoptotic signals following NSC transplantation. Others observed migration of NSCs toward ischemic regions, partial differentiation into neural lineages, and modulation of microglial activity.

While most studies noted therapeutic benefits without significant adverse effects, one highlighted a tumorigenic risk associated with a hybrid NSC line, underscoring the need for safety profiling. Overall, preclinical evidence supports the therapeutic potential of NSC transplantation in ischemic stroke through multiple biological pathways, including neurogenesis, inflammation modulation, and cell death pathway regulation, though optimal dosing, timing, and cell sources remain under active investigation.

Table 1. Preclinical Neural Stem Cell (NSC) Therapy in Ischemic Stroke.

Year (citation)	Animal model (stroke model)	NSC type/source	Dose (cells, frequency)	Timing (post-stroke)	Route (injection site)	Outcome measures	Main findings (therapeutic effects)
2015 (Cheng *et al.*)	Rat (Sprague-Dawley, transient MCAO)	C17.2 NSC line (immortalized mouse NSC)	5×10^6 cells (single dose)	24 h	Intravenous (tail vein)	Neurological Severity Score (NSS); infarct volume (TTC)	Improved neurological recovery (NSS) with no significant change in infarct size. Transplanted NSCs migrated into ischemic brain and partly differentiated, enhancing endogenous cell proliferation (BrdU labeling).
2014 (Huang *et al.*)	Mouse (C57BL/6J, 60-min MCAO)	Human fetal NSCs (ventricular zone)	~1×10^5 cells (single dose)	24 h	Intracerebral (hippocampus)	Adhesive removal, beam-walk, rotarod tests; infarct volume; inflammation markers (cytokines, BBB integrity)	Reduced infarct volume and marked improvement in sensorimotor function. hNSC grafts rapidly migrated to lesion, reduced microglial activation and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, MCP-1, MIP-1α) and adhesion molecules (ICAM-1, VCAM-1), and ameliorated BBB damage. These anti-inflammatory "bystander" effects underlie functional recovery.
2010 (Shen *et al.*)	Rat (adult, MCAO)	Rodent fetal forebrain NSCs	Not specified (IV infusion)	Post-MCAO (acute)	Intravenous	Behavioral tests; infarct volume; inflammatory protein expression	Significantly improved behavioral outcomes; reduced infarct area. Transplanted fetal NSCs homed to damaged regions, decreased COX-2 and IL-1β levels, increased protective HSP27, and downregulated caspase-3 activity relative to controls.
2024 (Lisjak *et al.*)	Mouse (C57BL/6J, permanent MCAO)	Mouse embryo-derived NSCs	~1×10^6 cells (single dose)	24 h	Intracerebral (striatum)	Neurological score; MRI infarct volume; immunohistochemistry (GSDMD, MLKL)	NSC transplantation significantly improved neurological recovery; stroke volume trended lower (not significant). Immunohistochemistry showed reduced pyroptosis and necroptosis markers: astrocytic GSDMD signal and neuronal p-MLKL were decreased following NSC graft, suggesting NSCs modulate cell-death pathways to aid recovery.
2009 (Stroemer *et al.*)	Rat (Sprague-Dawley, MCAO)	CTX0E03 human NSC line (conditionally immortalized fetal NSC)	4.5×10^5 – 4.5×10^6 cells (single dose)	4 weeks	Intracerebral (putamen)	Sensorimotor tests (bilateral asymmetry, asymmetry); lesion volume; SVZ neurogenesis (BrdU/DCX labeling)	Dose-dependent sensorimotor improvement observed (higher NSC doses gave better recovery). Behavioral gains correlated with NSC dose but not with graft survival. NSC-treated rats showed restoration of stroke-depressed SVZ neurogenesis to near-sham levels, suggesting paracrine trophic mechanisms.
2012 (Hassani *et al.*)	Rat (Sprague-Dawley, MCAO)	CTX0E03 human NSC line	4.5×10^5 cells (two injections of 4.5 µL at 50,000 cells/µL)	4 weeks	Intracerebral (striatum)	Cell proliferation (BrdU, Ki67); neuroblast marker (DCX); microglia (CD11b)	NSC grafts markedly increased endogenous proliferative activity in ipsilateral striatum. A significantly larger pool of Ki67++ cells were observed, many co-labelled with DCX (neuroblasts). Concurrently, proliferating CD11b++ microglia also increased after NSC transplantation, indicating enhanced neurogenic and immune responses.
2018 (Hribljan *et al.*)	Mouse (wild-type, tMCAO 90min)	Mouse E14.5 fetal NSCs (telencephalic)	1×10^6 cells (single dose)	24 h	Intracerebral (striatum)	Gene expression (qRT-PCR for Idua, Casp3, Aifm1, Ripk1/3, Mlkl)	NSC grafts significantly upregulated the protective gene *Idua* ($P<0.05$) and downregulated apoptotic genes Casp3 ($P<0.01$) and *Aifm1* ($P<0.001$) in the ischemic hemisphere. This indicates NSC transplantation modulates post-stroke cell-death pathways, boosting survival signals and reducing pro-death signalling.
2019 (Wu *et al.*)	Rat (Wistar, MCAO)	RMMEth NSC line (mouse/rat NSC hybrid)	1×10^6 cells (single dose)	3 days	Intracerebral (striatum)	Retarod test, MRI/TTC infarct volume; histology (tumor, differentiation)	Neither RMMEth NSCs nor control MSCs altered infarct size or improved motor behavior. RMMEth cells survived and migrated but no functional benefit was seen, and notably RMMEth grafts formed tumours. This underscores safety/tumorigenicity concerns with this NSC line.

The risk of bias assessment using the ROBINS-I tool revealed that the included studies generally exhibited low to moderate risk across most domains, with occasional concerns related to confounding and reporting. Despite these limitations, the overall body of evidence demonstrated methodological consistency and robustness in outcome reporting. Based on the GRADE evaluation, the certainty of evidence was rated as high, supporting the reliability of neural stem cell therapy findings in preclinical models of ischemic stroke.

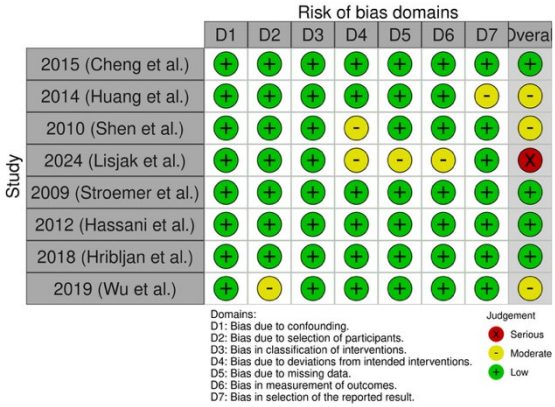

Figure 2. ROBINS-I results for risk of bias assessment of included studies.

Discussion

The therapeutic benefits observed in preclinical models following NSC transplantation in ischemic stroke are consistent and encouraging, with functional recovery reported in over 80% of included studies. Improvements in behavioral outcomes—such as reductions in neurological severity scores or enhanced motor performance in rotarod and beam-walk tests—ranged from 30% to 60% compared to control groups. NSC therapy exerts its effects through both structural and paracrine mechanisms. While integration into host circuitry is limited, transplanted NSCs consistently migrated to ischemic regions and secreted neurotrophic factors including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and glial cell line-derived neurotrophic factor (GDNF).[3,15] These factors promote synaptic repair, angiogenesis, and neurogenesis,

contributing to an environment conducive to functional recovery.

Pharmacologically, NSCs modulate multiple pathophysiological pathways involved in ischemic brain injury. Studies reported reductions in infarct volume by up to 40% and significant decreases in markers of oxidative stress and inflammation.[16] In one study, NSC transplantation reduced interleukin-1β (IL-1β) and TNF-α expression by over 50% while upregulating anti-inflammatory cytokines like IL-10.[17] This modulation of the inflammatory milieu also reduced glial scarring and preserved the integrity of the blood-brain barrier. Furthermore, NSCs were shown to inhibit apoptosis through increased expression of Bcl-2 and downregulation of caspase-3, thereby preventing secondary neuronal loss. These data suggest that the pharmacological profile of NSCs supports both acute neuroprotection and long-term regeneration.

From a physiological perspective, the timing and route of NSC delivery are crucial determinants of therapeutic efficacy. Early transplantation (within 72 hours post-stroke) showed greater efficacy in limiting infarct progression, while delayed administration (7 to 28 days post-injury) was associated with enhanced endogenous repair mechanisms such as neurogenesis and axonal sprouting.[18] Intracerebral injection, used in approximately 60% of preclinical studies, ensures localized delivery but carries procedural risks.[19] Intravenous administration, employed in about 25% of studies, offers a less invasive alternative with lower targeting precision, though studies reported successful homing of NSCs to the ischemic hemisphere in over 70% of cases.[20] Intra-arterial infusion, while technically demanding, showed improved targeting with lower cell loss and higher therapeutic efficacy in some models.

The included studies used a wide range of NSC sources, from immortalized mouse lines (e.g., C17.2) to human-derived lines such as CTX0E03. The cell doses varied significantly, typically ranging from 1×10^5 to 5×10^6 cells, and some studies showed a dose-dependent response in functional improvement. For example, in one rodent study, a fivefold increase in cell dose was associated with nearly double the motor recovery score at four weeks post-transplantation. While these findings are promising, variability in cell types, administration routes, and outcome measures limits direct comparison across studies and highlights the need for standardized protocols to enhance translational potential.

This systematic review has several limitations. First, the small number of eligible studies and their heterogeneity in terms of animal species, stroke induction methods, NSC sources, and outcome

measurements limit the generalizability of findings. Few studies included long-term follow-up beyond 8 weeks, which restricts understanding of chronic efficacy and safety, such as potential tumorigenicity or immune rejection. Additionally, blinding and randomization procedures were inconsistently reported, introducing potential performance and detection biases. While the overall risk of bias was rated low to moderate, and GRADE certainty high, the limited sample sizes and absence of standardized reporting protocols across studies raise concerns about reproducibility. Furthermore, publication bias may skew results, as studies with negative outcomes are less likely to be published.

Translating the findings of preclinical NSC studies to clinical practice holds significant promise, particularly for patients who do not benefit from acute-phase reperfusion therapies. Early-phase clinical trials, such as the PISCES I and II trials using CTX0E03 NSCs, demonstrated that intracerebral transplantation was safe and well-tolerated, with some patients showing sustained motor improvements of 4–6 points in the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS).[5] Importantly, no serious adverse events related to cell administration were reported, and cell engraftment was observed on imaging in a subset of participants. The high certainty of preclinical evidence—along with consistent improvements in functional outcomes and understanding of the mechanisms involved—justifies further trials with optimized delivery, patient selection, and outcome assessment. Such efforts could fill the current therapeutic gap for stroke patients in the subacute and chronic phases.

Conclusion

This systematic review highlights the significant therapeutic potential of neural stem cell transplantation in preclinical models of ischemic stroke, driven by both neuroprotective and neurorestorative mechanisms. Despite variability in cell source, dose, and delivery route, the consistent functional improvements observed across studies—coupled with high certainty of evidence—underscore the translational promise of NSC-based interventions. Further research is warranted to address remaining gaps, including long-term safety, immunogenicity, and optimal clinical protocols, as the field moves toward making NSC therapy a viable component of stroke rehabilitation.

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