



The Role of Stem Cell Therapy in Stroke: A Narrative Review of Scientific Evolution, Clinical Evidence, and Implementation Challenges in Neurology

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ABSTRACT

Stroke represents a paramount challenge to global public health, standing as a primary cause of mortality and long-term adult disability. In Indonesia, the epidemiological shift toward younger populations and the escalating socioeconomic burden necessitate a transition from traditional neuroprotection to advanced neurorestoration. This narrative literature review provides an exhaustive analysis of the role of stem cell therapy in stroke management, synthesizing four decades of scientific evolution. The report delineates the biological foundations of neurorestoration—including neurogenesis, angiogenesis, synaptogenesis, and immunomodulation—while characterizing various stem cell sources such as mesenchymal stem cells (MSCs), neural stem cells (NSCs), and bone marrow mononuclear cells (BMMNCs). A rigorous methodological assessment using the Cochrane Risk of Bias tool is applied to major clinical trials, including the MASTERS and TREASURE programs. Results

indicate that while stem cell therapy demonstrates a robust safety profile and significant improvements in functional activities of daily living (measured by the Barthel Index and NIHSS), consistent global disability reduction (measured by mRS) remains elusive due to a translational disconnect involving dosage, timing, and delivery modalities. Furthermore, this review explores the multifaceted challenges of implementation within neurology practice, particularly in Indonesia, addressing ethical concerns regarding unproven therapies and the critical need for enhanced specialized education for neurologists. The synthesis concludes with strategic recommendations for integrating regenerative medicine into clinical pathways to bridge the current therapeutic gap.

INTRODUCTION

Introduction: The Global and Indonesian Stroke Crisis

The landscape of cerebrovascular disease has undergone a dramatic transformation in the 21st century. Stroke is no longer a condition confined to the elderly; it has become an egalitarian threat affecting productive-age individuals with increasing frequency. Globally, the burden of stroke is immense, but in Indonesia, the statistics reveal a particularly acute crisis. According to the 2023 Global Burden of Disease (GBD) data, stroke is the leading cause of death in the archipelago, contributing to approximately 6.7 million healthy life years lost, measured as Disability-Adjusted Life Years (DALYs).¹ This burden is driven by a complex interplay of non-modifiable factors—such as age, gender (with women showing slightly higher vulnerability), and family history—and a surge in modifiable metabolic and behavioral risks.¹

In Indonesia, the demographic profile of stroke patients is notably younger than global averages. Statistics indicate that 66% of stroke cases occur in people under the age of 70, compared to 63% globally.¹ Since 1990, there has been a staggering 100% increase in the number of individuals suffering from stroke before age 70 in Indonesia.¹ This shift has profound implications for the national economy and household stability. Data from the Indonesian Health Insurance (BPJS) shows that stroke healthcare costs rose from 1.43 trillion Rupiah in 2016 to 2.57 trillion Rupiah in 2018, highlighting the financial strain on the public health system.²

The underlying risk factors in the Indonesian population are uniquely distributed. High systolic blood pressure accounts for nearly 60% of the stroke burden, while other major contributors include high Body Mass Index (BMI), fasting plasma glucose, and poor dietary habits characterized by high sodium and red meat consumption.¹ Behavioral factors such as smoking (affecting 76.2% of men) and low levels of physical activity (reported by 37.4% of the population over age 10) further exacerbate the risk.¹ Environmental factors have also emerged as critical determinants; air pollution, particularly household air pollution, is now recognized as a significant driver of stroke incidence in

Indonesia.¹

Despite the prevalence of these risks, the current acute management options remain limited. Intravenous thrombolysis (IVT) with recombinant tissue-type plasminogen activator (tPA) is the gold standard but is constrained by a narrow 4.5-hour window.⁴ Mechanical thrombectomy (MT) has extended the window for large vessel occlusions up to 24 hours, yet its implementation is hindered by a lack of specialized neurointerventionalists and a deficiency of CT scan machines and stroke units in rural areas.² Only a small fraction of patients—less than 15% in many settings—qualify for these recanalization therapies.⁵ This leaves a vast majority of survivors with persistent neurological deficits, creating a desperate need for neurorestorative therapies that can promote brain repair beyond the acute phase.

The Socioeconomic and Clinical Gap

The clinical gap between acute intervention and long-term recovery is where stem cell therapy offers the most promise. While reperfusion aims to salvage the ischemic penumbra, it cannot replace the lost neuronal architecture in the infarcted core. Stroke survivors often face life-altering impairments that affect their ability to maintain religious duties, contribute to their families, and maintain their quality of life.² Caregivers, in turn, experience significant psychological distress, including anger, disappointment, and pity.² As the "golden period" for acute treatment closes, a second epoch of endogenous repair begins, lasting days to weeks.⁹ It is during this window that neurorestorative therapies—specifically cell-based interventions—target the biological substrates of recovery.⁹

Epidemiological of Stroke Burden (Indonesia)

Metric	Indonesia
Age-Standardized Mortality (per 100k)	193.3

DALYs Lost (per 100k)	3,382.2
Stroke Prevalence (Urban)	0.022%
Stroke Prevalence (Rural)	0.0017%
BPJS Cost (2018)	2.57 Trillion IDR
Smoking Prevalence (Men)	76.2%

Pathophysiology and the Neurorestorative Paradigm

The biological rationale for stem cell therapy in stroke is rooted in the complex molecular cascade that follows cerebral ischemia. When blood flow is interrupted, a sequence of events—excitotoxicity, oxidative stress, and rapid metabolic failure—leads to a necrotic core.⁸ However, the surrounding tissue remains in a state of flux. The neurorestorative paradigm shifts the focus from preventing this immediate death to amplifying the brain's intrinsic repair mechanisms.¹⁰

The Neurovascular Unit and Endogenous Repair

Recovery post-stroke involves the coordinated action of neurons, astrocytes, oligodendrocytes, and cerebral endothelial cells—collectively referred to as the neurovascular unit.¹⁰ Neurorestoration is achieved by enhancing three primary processes: neurogenesis (generation of new parenchymal cells), angiogenesis (formation of new blood vessels), and oligodendrogenesis (restoration of myelin and signal transduction).⁹

Ischemia itself triggers a compensatory response. Neural stem cells in the subventricular zone (SVZ) of the brain proliferate and migrate toward the ischemic boundary.¹² This migration is

guided by chemokines like stromal-derived factor 1alpha (SDF-1alpha) and its receptor CXCR4, which are up-regulated in the activated endothelial cells of the peri-infarct area.¹² Furthermore, matrix metalloproteinases (MMPs), specifically MMP2 and MMP9, degrade the extracellular matrix to facilitate the movement of these neuroblasts.¹²

Stem cell therapy aims to bolster these endogenous pathways. Unlike neuroprotective drugs that failed in clinical trials because they targeted single molecular pathways during the hyper-acute phase, stem cells act as multi-modal "biological pumps".⁹ They secrete a wide array of neurotrophic factors, including BDNF, GDNF, and Nerve Growth Factor (NGF), which prevent apoptosis, support synaptic connectivity, and limit the secondary glial reaction.⁸ This "bystander effect" is now recognized as a primary mechanism of action, often more significant than the direct replacement of dead neurons.⁸

Molecular Mechanisms of Stem Cell Action

Mechanism	Description	Primary Mediators
Neurogenesis	Generation of new neurons from NSCs and progenitor cells.	BDNF, GDNF, NGF
Angiogenesis	Sprouting of new capillaries to restore microcirculation.	VEGF, Angiopoietin-1, bFGF
Oligodendrogenesis	Remodeling of white matter and promotion of myelination.	Trophic factors

Immunomodulation	Suppression of harmful neuroinflammation and M1 to M2 macrophage shift.	Cytokines, Exosomes, MicroRNAs
Synaptogenesis	Rewiring of surviving neural circuits to restore function.	Synaptic remodeling factors

METHODS

Review Framework and Quality Assessment

This report is based on a narrative literature review of clinical evidence and preclinical foundations published between 2000 and 2025. The search strategy targeted key databases including PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. Keywords utilized included "stem cell therapy," "ischemic stroke," "neurorestoration," "clinical trials," and "neurological outcomes."

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Stroke patients	Stem cell therapy	Standard stroke therapy	Functional recovery
Keyword 2	Ischemic stroke patients	Cell-based therapy	Conventional rehabilitation	Neurological improvement

				(NIHSS, mRS)
Keyword 3	Stroke survivors	Stem cell transplantation	Pharmacological neuroprotection	Safety and adverse events
Keyword 4	Patients with cerebrovascular accident (CVA)	Regenerative medicine for stroke	Placebo or control group	Quality of life post-stroke

The Boolean MeSH keywords inputted on databases for this research are: (*"Stroke patients" OR "Ischemic stroke patients" OR "Stroke survivors" OR "Patients with cerebrovascular accident" OR "Post-stroke patients"*) AND (*"Stem cell therapy" OR "Cell-based therapy" OR "Stem cell transplantation" OR "Regenerative medicine" OR "Mesenchymal stem cell therapy"*) AND (*"Standard stroke therapy" OR "Conventional rehabilitation" OR "Pharmacological neuroprotection" OR "Placebo" OR "Control group"*) AND (*"Functional recovery" OR "Neurological improvement" OR "Safety profile" OR "Adverse events" OR "Quality of life post-stroke"*)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Stroke patients" OR "Ischemic stroke patients" OR "Stroke survivors" OR "Patients with cerebrovascular accident" OR "Post-stroke patients") AND ("Stem cell therapy" OR "Cell-based therapy" OR "Stem cell transplantation" OR "Regenerative medicine" OR "Mesenchymal stem cell therapy") AND ("Standard stroke therapy" OR "Conventional rehabilitation" OR "Pharmacological neuroprotection" OR "Placebo" OR "Control group") AND ("Functional recovery" OR "Neurological improvement" OR "Safety profile" OR "Adverse events" OR "Quality of life post-stroke")	25
Semantic Scholar	("Stroke patients" OR "Ischemic stroke patients" OR "Stroke survivors" OR "Patients with cerebrovascular accident" OR "Post-stroke patients") AND ("Stem cell therapy" OR "Cell-based therapy" OR "Stem cell transplantation" OR "Regenerative medicine" OR "Mesenchymal stem cell therapy") AND ("Standard stroke therapy" OR "Conventional rehabilitation" OR "Pharmacological neuroprotection" OR "Placebo" OR "Control group") AND ("Functional recovery" OR "Neurological improvement" OR "Safety profile" OR "Adverse events" OR "Quality of life post-stroke")	250
Springer	("Stroke patients") AND ("Stem cell therapy") AND ("Standard stroke therapy" OR "Conventional rehabilitation" OR "Pharmacological neuroprotection" OR "Placebo" OR "Control group") AND ("Functional recovery" OR "Neurological improvement" OR "Safety profile" OR "Adverse events" OR "Quality of life post-stroke")	239
Google Scholar	("Stroke patients" OR "Ischemic stroke patients" OR "Stroke survivors" OR "Patients with cerebrovascular accident" OR "Post-stroke patients") AND ("Stem cell therapy" OR "Cell-based therapy" OR "Stem cell transplantation" OR "Regenerative medicine" OR "Mesenchymal stem cell therapy") AND ("Standard stroke therapy" OR "Conventional rehabilitation" OR "Pharmacological neuroprotection" OR "Placebo" OR "Control group") AND ("Functional recovery" OR "Neurological improvement" OR "Safety profile" OR "Adverse events" OR "Quality of life post-stroke")	1
Wiley Online Library	("Stroke patients") AND ("Stem cell therapy") AND ("Standard stroke therapy" OR "Conventional rehabilitation" OR "Pharmacological neuroprotection" OR "Placebo" OR "Control group") AND ("Functional recovery" OR "Neurological improvement" OR "Safety profile" OR "Adverse events" OR "Quality of life post-stroke")	6

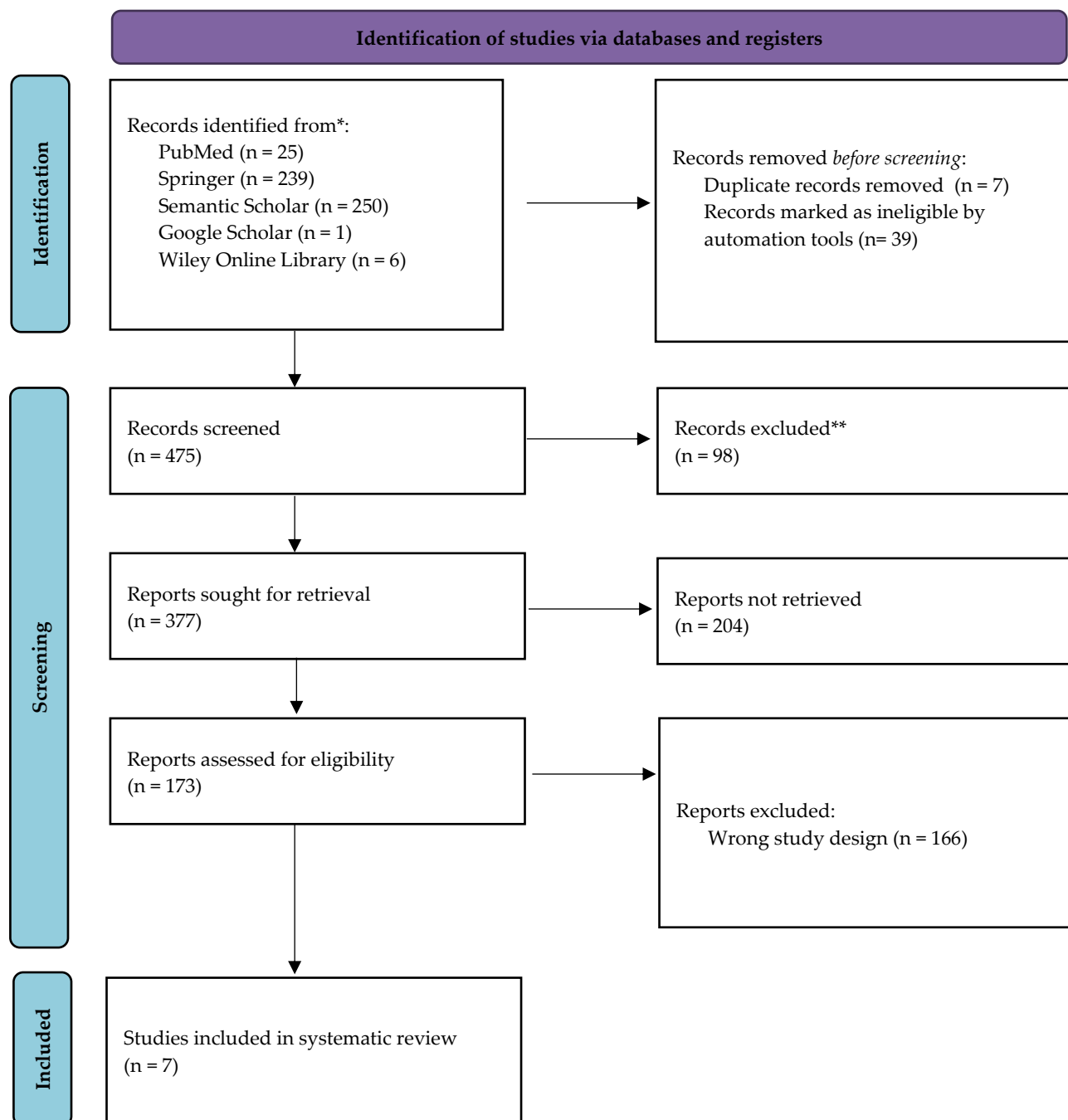


Figure 1. Article search flowchart

Cochrane Risk of Bias Assessment

To ensure a critical understanding of the evidence, major randomized controlled trials (RCTs) in the field were evaluated using the Cochrane Risk of Bias (RoB) tool. This assessment focuses on seven domains of potential bias that can impact the internal validity of clinical findings.⁷

Cochrane Risk of Bias Summary for Major Stem Cell Trials

Trial/Stu dy	Random Sequence Generati on	Allocatio n Conceal ment	Perform ance Bias (Blinding)	Detection Bias (Outcom e Assessme nt)	Attrition Bias (Incompl ete Data)	Reportin g Bias (Selective Outcome s)
Bang 2005	Low	Unclear	High	Low	High	Low
Prasad 2014	Low	Low	High	Low	Low	High
MASTE RS-1 (2017)	Low	Low	Low	Low	Low	Low
TREASU RE	Low	Low	Low	Low	Low	Low

(2024)						
PISCES-1 (2016)	N/A	N/A	High	Low	Low	Low
STARTING (2010)	Low	Low	High	Low	Low	Low
InveST (2014)	Low	Low	High	Low	Low	High

The assessment reveals a notable evolution in trial quality. Early studies, such as the Bang (2005) trial, frequently suffered from attrition bias—in that case, 40% of the control group was lost—and a high risk of performance bias due to a lack of blinding.¹⁸ Similarly, several mid-decade trials such as InveST failed to report all primary outcomes as listed in their methods, leading to reporting bias.¹⁸ However, the most recent large-scale trials, such as MASTERS-1 and TREASURE, have successfully implemented double-blind, placebo-controlled designs that significantly reduce these risks.¹⁹ Despite these improvements, the Cochrane review still categorizes the certainty of evidence as "low" because of the small sample sizes in most trials (often fewer than 32 participants) and the presence of high heterogeneity in outcome measures.⁷

LITERATURE REVIEW

Characterization of Stem Cell Types

The therapeutic potential of cell therapy depends heavily on the cell source, each offering

distinct biological advantages and logistical challenges.

Mesenchymal Stem Cells (MSCs)

MSCs are the most extensively studied cells in the context of stroke, appearing in over 52% of clinical trials.¹⁷ They can be derived from various tissues, including bone marrow (BMSCs), umbilical cord (UC-MSCs), and adipose tissue (ADSCs).⁸ MSCs are favored for their:

- **Accessibility and Scalability:** They can be easily isolated and expanded in vitro, with umbilical cord sources providing a more "naive" and proliferative cell population than adult bone marrow.¹⁷
- **Safety Profile:** MSCs are hypoimmunogenic, meaning they can be used for allogeneic (donor-derived) transplantation without the need for intensive immunosuppression.¹⁹
- **Paracrine Potency:** Their primary mechanism is not cell replacement but the secretion of trophic factors and extracellular vesicles (EVs) that dampen inflammation and promote angiogenesis.¹⁵

Neural Stem Cells (NSCs)

NSCs are multipotent cells that naturally differentiate into neurons, astrocytes, and oligodendrocytes.⁸ Their therapeutic appeal lies in their high neurogenic potential and their ability to integrate into existing neural circuits.²³ However, their use is complicated by ethical concerns regarding fetal-derived cells and the risk of tumor formation in induced pluripotent stem cell (iPSC)-derived versions.¹⁵ Clinical trials like PISCES have explored stereotactic intracranial injection of NSCs in chronic stroke, showing a favorable safety profile but achieving only modest functional gains.²⁴

Bone Marrow Mononuclear Cells (BMMNCs)

BMMNCs are a heterogeneous population of cells harvested from the bone marrow, including hematopoietic stem cells and endothelial progenitor cells.⁵ Their advantage is that they can be harvested and infused within a "point-of-care" setting without the need for lengthy ex vivo

cultivation.²⁷ However, the regenerative potential of autologous BMMNCs is limited in elderly patients, whose bone marrow cells often show signs of senescence and decreased proliferative capacity.¹⁵

Induced Pluripotent Stem Cells (iPSCs)

iPSCs represent the cutting edge of regenerative medicine. By reprogramming somatic cells to a pluripotent state, researchers can create patient-specific cell lines that eliminate the risk of immune rejection.⁸ While they show remarkable results in animal models—reducing infarct size and promoting neuronal survival—the translation to humans is currently hindered by high manufacturing costs and the risk of teratoma formation.⁸

Comparison of Stem Cell Types in Stroke Therapy

Stem Cell Type	Source	Advantages	Disadvantages	Primary Target Window
BMSCs	Bone Marrow	Well-documented safety, paracrine support	Invasive harvest, age-related decline	Subacute/Chronic
UC-MSCs	Umbilical Cord	"Off-the-shelf," high proliferation	Regulatory hurdles for allogeneic use	Acute/Subacute

BMMNCs	Bone Marrow	Rapid administration, autologous	Limited potency in elderly ¹⁵	Acute (24-72h)
NSCs	Fetal/iPSC	High neurogenic potential	Ethical/Invasive (IC injection)	Chronic
iPSCs	Somatic cells	Personalized, unlimited supply	Teratoma risk, extremely expensive	Experimental

Synthesis of the Clinical Trial Landscape

The progression of stem cell clinical trials has moved from Phase I feasibility studies to Phase II/III pivotal trials. While safety has been established across virtually all types of stem cell interventions, efficacy has been inconsistent.

The MultiStem Program: MASTERS-1 and MASTERS-2

The MASTERS-1 trial was a Phase II, multicenter, randomized study evaluating allogeneic MultiStem (MAPCs) delivered intravenously in acute stroke patients within a 24-48 hour window.¹⁵ The primary endpoint—achieving an "Excellent Outcome" at 90 days (mRS ≤ 1 , NIHSS ≤ 1 , and BI ≥ 95)—was not statistically significant for the whole population.¹⁹ However, a critical post-hoc analysis revealed that patients treated within 36 hours of stroke onset showed a significantly higher rate of functional independence at 90 days and even greater improvements at one year ($p < 0.01$).¹⁹ This finding emphasized that "timing is brain" even for regenerative therapies.

MASTERS-2 is an ongoing Phase III pivotal trial designed to confirm these findings in a larger cohort of 300 patients, specifically targeting the 18-36 hour window.¹⁹ As of late 2023, the trial had enrolled more than half of its expected participants across North America and Europe.²²

The TREASURE Trial

The TREASURE trial in Japan provided a real-world test for MultiStem in an older demographic (mean age 76.5).²⁰ Like MASTERS-1, the primary endpoint of "Excellent Outcome" at 90 days was not reached (11.5% in MultiStem vs. 9.8% in placebo, $p = 0.90$).²⁰ However, there was a measurable "mRS shift" and significant improvement in "Global Recovery" measures at the one-year mark.²⁹ Subgroup analysis suggested that younger patients (under age 64) and those with an ischemic core volume of 50 mL or less derived the most benefit.³⁰ These results suggest that while the stringent "Excellent Outcome" composite may be difficult to reach in elderly populations, functional independence (mRS ≤ 2) is a more achievable and clinically relevant target.²⁹

The Indonesian Contribution: Case Report of hUC-MS

In a notable application within Indonesia, a 53-year-old male with sudden-onset left-sided weakness and an initial NIHSS of 11 received adjuvant therapy of allogenic human umbilical cord mesenchymal stem cells (hUC-MSCs).³² The patient received 30 million cells on the fourth day after stroke onset, with a repeat dose three weeks later.³² At the three-week follow-up, the patient showed dramatic improvement, with his NIHSS score dropping from 11 to 3, allowing him to walk independently despite persistent motor weakness.³² This case underscores the potential of UC-MSCs as a safe and effective "add-on" to standard treatment in the Indonesian clinical setting.

Summary of Key Clinical Trial Outcomes

Trial (Author/Year)	Cell Type	Route	Population	Outcome Highlights
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Bang et al. (2005)	Autologous MSCs	IV	Chronic	Improved recovery in 1- year follow-up ²¹
Prasad et al. (2014)	BMMNCs	IV	Subacute	Multicentric study; demonstrated safety ¹⁷
MASTERS-1 (2017)	MultiStem	IV	Acute	Positive post- hoc for early (< 36h) treatment ¹⁹
TREASURE (2024)	MultiStem	IV	Acute	Primary not sig; favorable at 1 year in younger/large core ²⁹
PISCES (2016)	NSCs	IC	Chronic	Safe; trend toward motor improvement ²⁴
STARTING (2010)	Autologous MSCs	IV	Subacute	Safe; improved recovery over long term ¹⁵

InveST (2014)	BMMNCs	IV	Subacute	Failed to show significant efficacy ¹⁵
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Comparison of Delivery Modalities

Choosing the optimal route of administration is a balance between biological efficacy and patient safety.

Intravenous (IV) Delivery

IV infusion is the most common method (48.6% of trials) because it is minimally invasive and can be easily performed at the bedside.¹⁷ It allows for a wide distribution of cells that can respond to chemotactic signals from the brain.²⁷ The main drawback is the "pulmonary first-pass effect," where over 95% of cells become trapped in the lungs, spleen, and liver.²⁷ Despite this, IV delivery is thought to exert systemic immunomodulatory effects that may indirectly aid brain repair.²⁷

Intra-arterial (IA) Delivery

IA delivery involves injecting cells directly into the artery supplying the ischemic territory, typically via the same catheterization used for mechanical thrombectomy.³⁴ This route bypasses the peripheral filtration organs, leading to a much higher concentration of cells in the brain.²³ However, IA delivery carries risks of microvascular obstruction, potentially leading to new strokes if the cell dose or size is too large.³⁴ Safety depends critically on infusion speed and the preservation of arterial blood flow during the procedure.³⁴

Intracerebral (IC) and Intracisternal Delivery

IC transplantation involves direct stereotactic injection into the brain parenchyma, ensuring that cells reach the exact site of injury.²³ While it achieves the highest local cell retention (60%

compared to 1.5% for IV), it is highly invasive and carries significant surgical risks, including hemorrhage and seizures.²⁷ Intracisternal/ventricular routes are less invasive than IC but show variable cell migration to the ischemic site and can cause fever or meningeal irritation.²⁷

Comparative Metrics for Cell Delivery Routes

Route	Invasiveness	Brain Bioavailability	Main Advantage	Main Risk
Intravenous (IV)	Low	Very Low (< 1.5%)	Systemic immunomodulation, easy	Lung trapping
Intra-arterial (IA)	Medium	High	Targeted delivery, bypasses lungs	Micro-embolism, new stroke
Intracerebral (IC)	High	Highest (~ 60%)	Precise localization	Hemorrhage, seizures
Intranasal	Very Low	Moderate	Non-invasive, direct CNS access	Nasal irritation (experimental)

DISCUSSION

The Translational Gap and Implementation Hurdles

Despite consistent safety data and promising mechanism-of-action studies, stem cell therapy has not yet been established as a standard of care. This "translational gap" is the result of several factors.

Dosage and Timing Discrepancies

Preclinical models in rats often show robust recovery using cell doses that, when scaled to humans, would require approximately 840 million cells for a 75kg adult.¹³ However, many clinical trials have used much lower doses—for instance, the SB623 trial used doses ten-fold below this efficacious threshold.¹³ Additionally, the timing of intervention is crucial. While neurorestoration targets a broader window than thrombolysis, the MultiStem data suggests that even within the "regenerative epoch," earlier treatment (under 36 hours) is significantly more effective than treatment at 48 hours.⁹

Patient Heterogeneity and Comorbidities

The majority of preclinical stroke research is conducted on young, healthy rodents. In contrast, the average stroke patient—particularly in Indonesia—is elderly and suffers from multiple comorbidities such as hypertension, diabetes, and obesity.¹ These conditions not only affect the brain's baseline repair capacity but also degrade the potency of the patient's own (autologous) stem cells.¹⁵ This provides a strong rationale for the shift toward allogeneic "off-the-shelf" products derived from younger, healthier donors.¹⁷

The Pseudoscience and Ethical Challenge

The excitement surrounding stem cell research has unfortunately led to a global rise in the commercial promotion of unsupported therapeutic uses—often termed "stem cell tourism" or "pseudoscience".³⁵ Clinics often market unproven "mesenchymal treatments" or "exosome

therapies" as immune boosters for a variety of conditions, including stroke, without rigorous clinical data.³⁷ This direct-to-consumer marketing can expose patients to severe risks, including infection and financial exploitation.³⁷

Ethically, the framing of stem cell therapy as a "miracle cure" can foster false hope and erode public trust in legitimate scientific institutions.³⁹ In Indonesia, where the healthcare system is undergoing transformation, distinguishing between authorized clinical trials and unproven commercial ventures is essential for patient safety.³⁵

Educational Imperatives in Neurology

For stem cell therapy to be successfully implemented, the next generation of neurologists must be equipped with research literacy and technical expertise. Current evidence suggests a significant knowledge gap; a study of medical students found that over 50% had "very poor" knowledge regarding the applications of stem cells in neurological disease.⁴⁰ In Indonesia, organizations like the Indonesian Neurologist Association (PERDOSNI) are addressing this by integrating neuroscience and neurorestorative approaches into their national curriculum and scientific meetings, such as PIN 2025 and COMEON 2025.⁴¹ Enhancing residency training to include the business, ethical, and scientific aspects of regenerative medicine is critical for the future of the field.⁴³

Policy and Implementation: The Indonesian Path Forward

Indonesia faces a unique set of challenges in managing the stroke epidemic. The uneven distribution of neurologists and medical facilities—with 60% of the population residing on the island of Java—necessitates innovative service models.²

1. **Strengthening Referral and Infrastructure:** The Indonesian government is currently increasing the number of Puskesmas (community health centers) and encouraging all hospitals to acquire CT scan machines and established stroke units.² This infrastructure is a prerequisite for both acute care and the eventual delivery of cell therapies.

2. **Regulatory Oversight:** There is a need for a coordinated national approach to regulate the marketing of cell-based products. Strengthening the enforcement of scientific standards for stem cell clinics will protect patients from unproven therapies.³⁵
3. **Harnessing Allogeneic Solutions:** Given the logistical difficulties of harvesting and culturing autologous cells in a developing economy, allogeneic "off-the-shelf" products like UC-MSCs offer a more scalable and cost-effective solution for a geographically dispersed population.²²
4. **Promoting Primary Prevention:** While stem cell therapy offers hope for recovery, primary prevention remains the most effective way to reduce the stroke burden. Strategies to control blood pressure, reduce smoking rates, and mitigate air pollution must remain the cornerstone of Indonesian health policy.¹

CONCLUSION

The role of stem cell therapy in stroke management has evolved from a theoretical concept to a promising, albeit complex, clinical reality. The scientific rationale for neurorestoration is robust, demonstrating that stem cells can modulate the ischemic environment through multiple synergistic mechanisms—primarily immunomodulation and the secretion of neurotrophic factors. Clinical evidence from major trials like MASTERS and TREASURE confirms the safety and feasibility of cell-based interventions and suggests significant functional benefits, particularly when administered within a precise 36-hour window or to specific patient subgroups.

However, the path to implementation in neurology practice is obstructed by the translational gap between animal models and elderly human patients, the proliferation of unproven pseudoscientific treatments, and a lack of specialized education. In Indonesia, where the stroke burden is escalating among younger populations, the integration of regenerative medicine into the standard of care is a public health necessity. Success will depend on the development of standardized protocols, the scaling of allogeneic cell products, and a renewed focus on educating neurologists to navigate the scientific and ethical frontiers of this new therapeutic epoch. Stem cell therapy should not be viewed as a standalone "cure," but as a biological catalyst that, when

combined with rigorous rehabilitation and modern acute care, offers a new horizon for stroke survivors worldwide.

REFERENCES

1. Utilizing Disease Burden Data for Health Policy Transformation - Badan Kebijakan Pembangunan Kesehatan, diakses Desember 31, 2025, <https://www.badankebijakan.kemkes.go.id/en/pemanfaatan-data-beban-penyakit-untuk-transformasi-kebijakan-kesehatan/>
2. Stroke Burden and Stroke Services in Indonesia - PMC - PubMed Central, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC9149342/>
3. Physical Activity of the Indonesian Population - Health Development Policy Agency, diakses Desember 31, 2025, <https://www.badankebijakan.kemkes.go.id/en/aktifitas-fisik-penduduk-indonesia/>
4. Thrombolysis for Ischemic Stroke Beyond the 4.5-Hour Window: A Meta-Analysis of Randomized Clinical Trials, diakses Desember 31, 2025, <https://www.ahajournals.org/doi/10.1161/STROKEAHA.124.048536>
5. Stem Cell–Based Therapies via Different Administration Route for Stroke: A Meta-analysis of Comparative Studies - NIH, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC11808770/>
6. Evidence review for thrombectomy - NCBI Bookshelf - NIH, diakses Desember 31, 2025, <https://www.ncbi.nlm.nih.gov/books/NBK577865/>
7. Stem cell transplantation for ischemic stroke - Cochrane, diakses Desember 31, 2025, https://www.cochrane.org/evidence/CD007231_stem-cell-transplantation-ischemic-stroke
8. Stem Cell Therapy for Stroke: A New Frontier in Neurodegenerative Medicines, diakses Desember 31, 2025, <https://www.ijpsjournal.com/article/Stem+Cell+Therapy+for+Stroke+A+New+Frontier+in+Neurodegenerative+Medicines>

9. Restorative Therapies after Stroke: Drugs, Devices, and Robotics, diakses Desember 31, 2025, <https://nams-annals.in/restorative-therapies-after-stroke-drugs-devices-and-robotics-2/>
10. Cell-based and pharmacological neurorestorative therapies for ischemic stroke - PMC, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC5832535/>
11. Clinical trials and advanced MRI techniques with stem cell therapy for ischemic stroke: present and future perspectives - PMC - NIH, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC12505762/>
12. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic - PMC - PubMed Central, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC2727708/>
13. Concise Review: Stem Cell Therapy for Stroke Patients: Are We ..., diakses Desember 31, 2025, <https://academic.oup.com/stcltm/article/8/9/983/6403776>
14. Neurorestorative Therapy for Stroke - PMC - PubMed Central - NIH, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC4072966/>
15. Adult Stem Cell Therapy for Stroke: Challenges and Progress - PMC, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC5066440/>
16. Post-Stroke Recovery with Stem Cell Therapy - Swiss Medica, diakses Desember 31, 2025, <https://www.startstemcells.com/stroke-treatment-and-recovery.html>
17. A narrative review on the role of stem cell therapy in stroke treatment ..., diakses Desember 31, 2025, <https://accscience.com/journal/AN/4/4/10.36922/an.5582>
18. Stem Cell Therapy in Ischemic Stroke: A Systematic Review and ..., diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC8232485/>
19. MultiStem - Clinical Trials - Ischemic Stroke - Athersys, Inc., diakses Desember 31, 2025, <https://www.athersys.com/multistem-therapy/clinical-trials/ischemic-stroke/default.aspx>
20. Allogeneic Stem Cell Therapy for Acute Ischemic Stroke: The Phase 2/3 TREASURE Randomized Clinical Trial - PubMed, diakses Desember 31, 2025, <https://pubmed.ncbi.nlm.nih.gov/38227308/>
21. Stem cell-based therapies for ischemic stroke: a systematic review and meta-analysis of

- clinical trials - ResearchGate, diakses Desember 31, 2025, https://www.researchgate.net/publication/342467874_Stem_cell-based_therapies_for_ischemic_stroke_a_systematic_review_and_meta-analysis_of_clinical_trials
22. Athersys Provides MultiStem Clinical Update, diakses Desember 31, 2025, <https://www.athersys.com/investors/press-releases/press-release-details/2023/Athersys-Provides-MultiStem-Clinical-Update/default.aspx>
23. Adult Stem Cells and Induced Pluripotent Stem Cells for Stroke Treatment - Frontiers, diakses Desember 31, 2025, <https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2019.00908/full>
24. Comparative study of the efficacy of intra-arterial and intravenous transplantation of human induced pluripotent stem cells-derived neural progenitor cells in experimental stroke - PubMed Central, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC10640846/>
25. Comparison of the Administration Route of Stem Cell Therapy for Ischemic Stroke: A Systematic Review and Meta-Analysis of the Clinical Outcomes and Safety - MDPI, diakses Desember 31, 2025, <https://www.mdpi.com/2077-0383/12/7/2735>
26. Study Details | NCT02425670 | Stem Cell Therapy For Acute Ischemic Stroke Patients | ClinicalTrials.gov, diakses Desember 31, 2025, <https://www.clinicaltrials.gov/study/NCT02425670>
27. Stem cell therapy in ischemic stroke: Role of IV and intra-arterial therapy - PMC - NIH, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC4109232/>
28. NCT03545607 | MultiStem® Administration for Stroke Treatment and Enhanced Recovery Study | ClinicalTrials.gov, diakses Desember 31, 2025, <https://www.clinicaltrials.gov/study/NCT03545607>
29. Overview of TREASURE Results, diakses Desember 31, 2025, [https://s23.q4cdn.com/674737627/files/doc_presentations/2022/ATHX-TREASURE-Slide-Story-FINAL-DRAFT-10a-\(002\).pdf](https://s23.q4cdn.com/674737627/files/doc_presentations/2022/ATHX-TREASURE-Slide-Story-FINAL-DRAFT-10a-(002).pdf)

30. MultiStem Cell Therapy Not Superior to Placebo in Patients With Ischemic Stroke | CGTlive®, diakses Desember 31, 2025, <https://www.cgtlive.com/view/multistem-cell-therapy-not-superior-to-placebo-ischemic-stroke>
31. Allogeneic Stem Cell Therapy for Acute Ischemic Stroke: The Phase 2/3 TREASURE Randomized Clinical Trial | Request PDF - ResearchGate, diakses Desember 31, 2025, https://www.researchgate.net/publication/377441434_Allogeneic_Stem_Cell_Therapy_for_Acute_Ischemic_Stroke_The_Phase_23_TREASURE_Randomized_Clinical_Trial
32. prosiding book jaknews 12 - Universitas Indonesia, diakses Desember 31, 2025, <https://ani.fk.ui.ac.id/index.php/journal/article/download/79/36>
33. Revisiting Stem Cell-Based Clinical Trials for Ischemic Stroke - PMC - PubMed Central, diakses Desember 31, 2025, <https://pmc.ncbi.nlm.nih.gov/articles/PMC7767918/>
34. Intra-Arterial Delivery of Cell Therapies for Stroke - American Heart Association Journals, diakses Desember 31, 2025, <https://www.ahajournals.org/doi/10.1161/STROKEAHA.117.018288>
35. Margaret Sleeboom-Faulkner PhD of Social Anthropology Professor at University of Sussex - ResearchGate, diakses Desember 31, 2025, <https://www.researchgate.net/profile/Margaret-Sleeboom-Faulkner>
36. The Scientific and Pseudoscientific Features of Smoking Cessation Products Which are Marketed on Internet - Scholars.Direct, diakses Desember 31, 2025, <https://scholars.direct/Articles/family-medicine/afmgp-5-027.php?jid=family-medicine>
37. Ethical issues and public communication in the development of cell-based treatments for COVID-19: Lessons from the pandemic - ResearchGate, diakses Desember 31, 2025, https://www.researchgate.net/publication/355342443_Ethical_issues_and_public_communication_in_the_development_of_cell-based_treatments_for_COVID-19_Lessons_from_the_pandemic
38. Chapter: Addressing Inaccurate and Misleading Information About Biological Threats Through Scientific Collaboration and Communication in Southeast Asia, diakses Desember 31, 2025, <https://www.nationalacademies.org/read/26466/chapter/3>

39. EACME Conference 2025 Book of Abstracts, diakses Desember 31, 2025, <https://www.ibme.uzh.ch/dam/jcr:a1467a25-76d2-488c-b23f-cd0d207b7289/EACME%20Conference%202025%20Book%20of%20Abstracts-.pdf>
40. Time to Revise the Medical Students' Educational Curriculum: Focus on New Therapeutic Strategies as Regenerative Medicine in Neurological Disorders - SID, diakses Desember 31, 2025, <https://www.sid.ir/FileServer/JE/50008120220113>
41. 2nd Announcement PIN PERDOSNI 2025 | PDF | Neurology | Electroencephalography - Scribd, diakses Desember 31, 2025, <https://www.scribd.com/document/841770557/2nd-Announcement-PIN-PERDOSNI-2025>
42. Final Announcement COMEON 2025 | PDF | Neurology | Stroke - Scribd, diakses Desember 31, 2025, <https://www.scribd.com/document/879096899/Final-Announcement-COMEON-2025>
43. Education Research: Neurology residency training in the new millennium - ResearchGate, diakses Desember 31, 2025, https://www.researchgate.net/publication/23950962_Education_Research_Neurology_residency_training_in_the_new_millennium