Stem Cells and Cloning: Advances and Applications

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REVIEW

Meta-Analysis: The Clinical Application of Autologous Adult Stem Cells in the Treatment of Stroke

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Introduction: Stroke is a leading cause of death and disability worldwide. The disease is caused by reduced blood flow into the brain resulting in the sudden death of neurons. Limited spontaneous recovery might occur after stroke or brain injury, stem cell-based therapies have been used to promote these processes as there are no drugs currently on the market to promote brain recovery or neurogenesis. Adult stem cells (ASCs) have shown the ability of differentiation and regeneration and are well studied in literature. ASCs have also demonstrated safety in clinical application and, therefore, are currently being investigated as a promising alternative intervention for the treatment of stroke.

Methods: Eleven studies have been systematically selected and reviewed to determine if autologous adult stem cells are effective in the treatment of stroke. Collectively, 368 patients were enrolled across the 11 trials, out of which 195 received stem cell transplantation and 173 served as control. Using data collected from the clinical outcomes, a broad comparison and a meta-analysis were conducted by comparing studies that followed a similar study design.

Results: Improvement in patients' clinical outcomes was observed. However, the overall results showed no clinical significance in patients transplanted with stem cells than the control population.

Conclusion: Most of the trials were early phase studies that focused on safety rather than efficacy. Stem cells have demonstrated breakthrough results in the field of regenerative medicine. Therefore, study design could be improved in the future by enrolling a larger patient population and focusing more on localized delivery rather than intravenous transplantation. Trials should also introduce a more standardized method of analyzing and reporting clinical outcomes to achieve a better comparable outcome and possibly recognize the full potential that these cells have to offer.

Keywords: adult stem cells, autologous, neurogenesis, inflammation, clinical application, stroke, stroke recovery, systematic review, meta-analysis

Introduction

Stroke is the second leading cause of death worldwide and one of the leading causes of disability.[1] The blockade or the rupture of a blood vessel to the brain leads to either ischemic or hemorrhagic stroke, respectively.[2,3] The extent and the location of the damaged brain tissue may be associated with irreversible cognitive impairment or decline in speech, comprehension, memory, and partial or total physical paralysis.[4]

Four chronological phases, namely hyperacute, acute, subacute, and chronic, describe the stroke's cellular manifestations.[5] The hyperacute phase is immediate and associated with glutamate-mediated excitotoxicity and a progressive neuronal

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death that can last a few hours.[6] The glutamate, a potent excitatory neurotransmitter, is also an inducer of neurodegeneration following stroke.[7] The acute phase, which could last over a week after the stroke, is associated with the delayed and progressive neuronal death and the infiltration of immune cells.[5] The following subacute phase can extend up to three months after the stroke and is mainly associated with reduced inflammation and increased plasticity of neurons, astrocytes, microglia, and endothelial cells, allowing spontaneous recovery.[8] In the chronic phase that follows, the plasticity of cells is reduced and only permits rehabilitation-induced recovery.[5]

The immediate treatments differ for ischemic and hemorrhagic strokes. Immediate intervention is required to restore the blood flow to the brain following an ischemic stroke. Thrombolytic agents, such as activase (Alteplase), a recombinant tissue plasminogen activator (tPA), are commonly given intravenously to dissolve the blood clots. Other more invasive approaches, such as a thrombectomy, use stents or catheters to remove the blood clot.[9] Antiplatelet agents like Aspirin, anticoagulants, blood pressure medicines, or statins are generally given to reduce the risk of recurrence. Some ischemic strokes are caused by the narrowing of the carotid artery due to the accumulation of fatty plaques; a carotid endarterectomy is performed to correct the constriction.

The treatment of a hemorrhagic stroke requires a different approach. An emergency craniotomy is usually performed to remove the blood accumulating in the brain and repair the damaged blood vessels. Accumulation of cerebrospinal fluid in brain ventricles (hydrocephalus) is also a frequent complication following a hemorrhagic stroke, which requires surgery to drain the fluid. Medications to lower blood pressure are given before surgery and to prevent further seizures.[10]

These immediate treatments are critical to minimize the long-term consequence of the stroke but do not address the post-stroke symptoms caused by neurodegeneration. New therapeutic approaches adapted to the physiology of each phase of the stroke are currently developed. A promising therapy has been the use of stem cells.[11] In this review, different clinical trials involving the use of various stem cells for the treatment of stroke are presented and compared using a meta-analysis of the published results.

Search Criteria

To narrow down the relevant literature, a search strategy focused on original literature and reporting the clinical application of stem cells in stroke was established. An NCBI PubMed word search for "stroke", "stem cells", and "adult stem cells" yielded 146 clinical studies between 2010 and 2021. Finally, 11 studies, using autologous adult stem cells in the treatment of stroke, were considered. A PRISMA flow diagram detailing an overview of the study selection procedure and the inclusion and exclusion of papers is included in Appendix I. The inclusion criteria comprise the injection of autologous adult stem cells at any stroke stages (hyperacute, acute, sub-acute, chronic), and clinical trials whose results have been published in the last 11 years. The exclusion criteria include studies published more than 11 years ago, studies not published in English, all preclinical studies, other diseases related to stroke (ex. cardiovascular diseases), embryonic or induced pluripotent stem cells, allogeneic stem cells, and other cell therapies. Two independent researchers reviewed and filtered the 146 studies by reading the titles and abstracts. All three authors approved the final selected studies.

Classification of Stem Cells Used to Treat Stroke

Stem cells are undifferentiated and unspecialized cells characterized by their ability to self-renew and their potential to differentiate into specialized cell types.[12] Ischemic stroke causes severe damage to the brain cells by destroying the heterogeneous cell population and neuronal connections along with vascular systems. The regenerative potential of several types of stem cells like embryonic stem cells, neural stem cells, adult stem cells (mesenchymal stem cells), and induced pluripotent stem cells have been assessed for treating stroke.

Adult stem cells exhibit multipotency and the ability to self-renew and differentiate into specialized cell types. They have been widely used in clinical trials and a safe option thus far in treating various diseases.[12,13,14] The plasticity of these cells allow their differentiation across tissue lineages when exposed to defined cell culture conditions.[15] There are multiple easily accessible sources of adult stem cells, mainly the bone marrow, blood, and adipose tissue. In clinical settings, both autologous and HLA-matched allogeneic cells have been transplanted and are deemed to be safe.

Adult stem cells can secrete a variety of bioactive substances into the injured brain following a stroke in the form of paracrine signals.[16–18] The paracrine signals include growth factors, trophic factors, and extracellular vesicles, which may be associated with enhanced

neurogenesis, angiogenesis, and synaptogenesis (Figure 1). Also, mesenchymal stem cells (MSCs) are thought to contribute to the resolution of the stroke by attenuating inflammation,[19] reducing scar thickness, enhancing autophagy, normalizing microenvironmental and metabolic profiles and possibly replacing damaged cells.[20]

A few routes of administration have been used to deliver the stem cells to the patients. The most common is through intravenous injection. Intra-arterial delivery is also performed; but this mode can be extremely painful to patients compared to an intravenous transfusion. The third approach is via stereotactic injections. This is an invasive surgery that involves injecting the cells directly into the site of affected in the brain.

Autologous Adult Stem Cells Used in Clinical Trials in the Treatment of Stroke

Mesenchymal Stem Cells (MSCs)

Also known as mesenchymal stromal cells or medicinal signaling cells, MSCs can be derived from different sources including bone marrow, peripheral blood, lungs, heart, skeletal muscle, adipose tissue, dental pulp, dermis, umbilical cord, placenta, amniotic fluid membrane and many more.[21] MSCs are characterized by positive cell surface markers, including Stro-1, CD19, CD44, CD90, CD105, CD106, CD146, and CD166. The cells are also CD14, CD34, and CD45 negative.[22,23] The cells are thought to provide a niche to stem cells in normal tissue and releases paracrine factors that promote neurogenesis (Figure 2).[19,20,24] During the acute and subacute stage of stroke, MSCs may inhibit inflammation, thus, reducing the incidence of debilitating damage and symptoms that may occur post-stroke.

Bone Marrow-Derived Mononuclear Cells (BM-MNC)

Derived from the bone marrow, mononuclear cells contain several types of stem cells, including mesenchymal stem cells and hematopoietic progenitor cells that give rise to hematopoietic stem cells and various other differentiated cells. They can produce and secrete multiple growth factors and cytokines. They are also attracted to the lesion or damage site where they can accelerate angiogenesis and promote repair endogenously through the proliferation of the hosts' neural stem cells. Mononuclear cells have also demonstrated the ability to decrease neurodegeneration, modulate inflammation, and prevent apoptosis in animal models.[25,26]

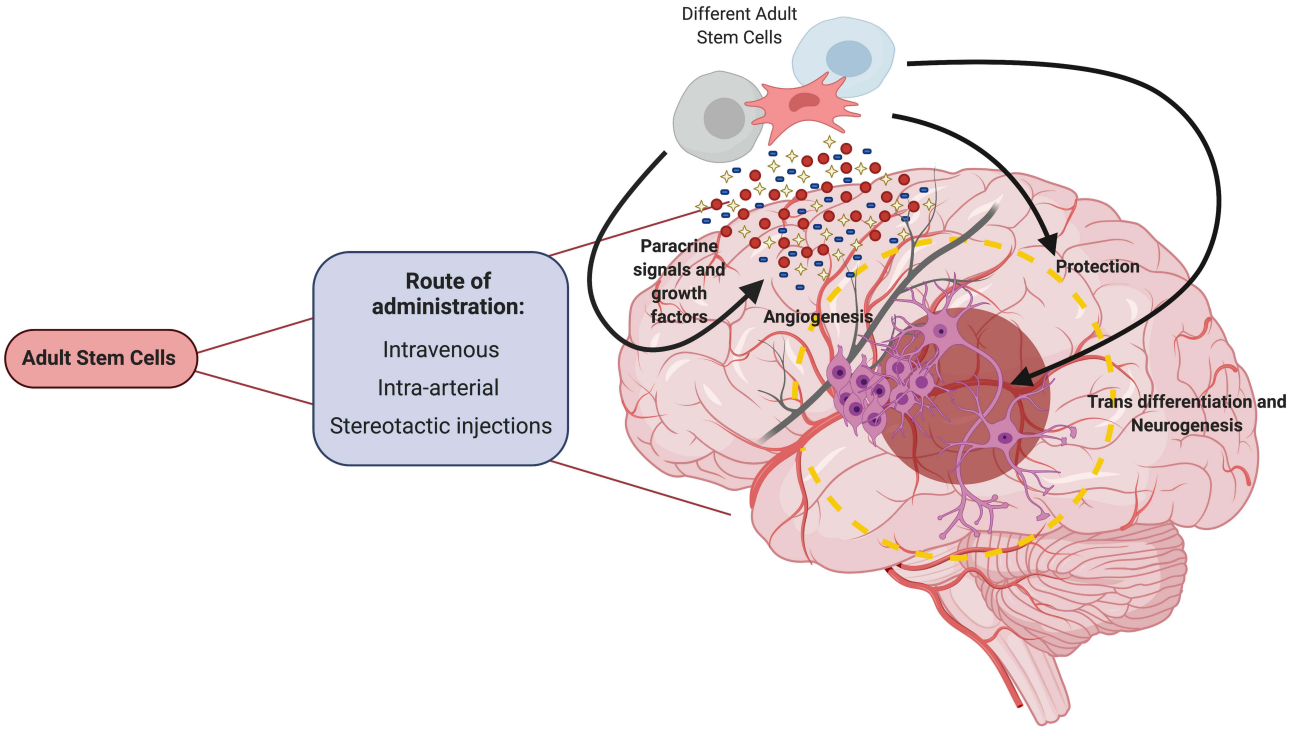

Figure 1 Schematic depicting the clinical application of different cells in stroke patients. The cells were delivered in one of three ways, intravenously, intra-arterially, or via stereotactic injections. Once administered, the cells play a role in providing paracrine signals and growth factors to facilitate angiogenesis and cell regeneration, immunomodulatory effects that serve to protect the neurons from further damage caused by inflammation, and finally, trans-differentiation of stem cells. Data from Dabrowska S, Andrzejewska A, Lukomska B, Janowski M.[19] Created with BioRender.com.

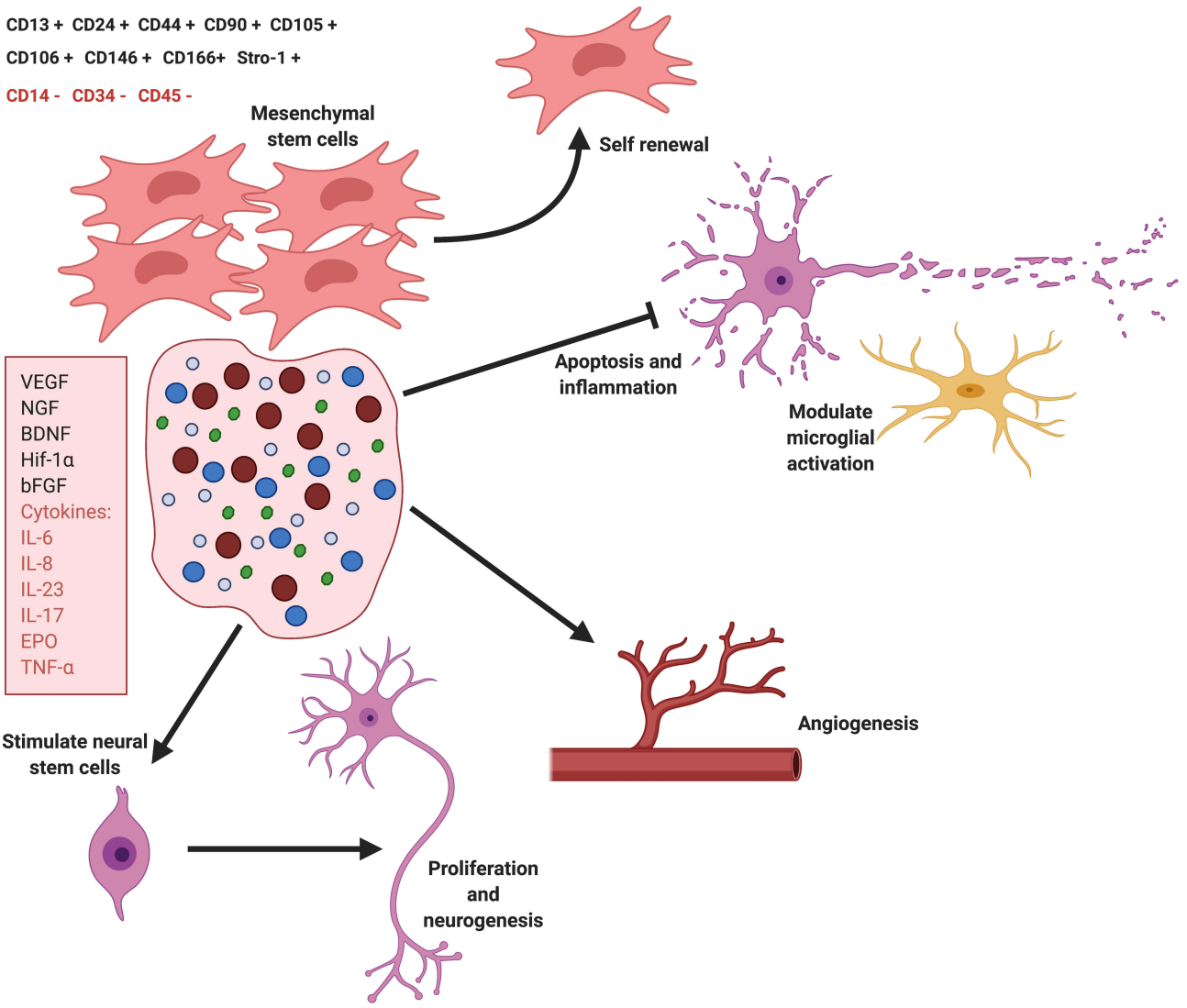

Figure 2 Schematic describing the role of mesenchymal stem cells in stroke. The cells release different growth factors, signals, and cytokines that serve to facilitate various functions. Through the release of cytokines, they can modulate inflammation and block apoptosis. The growth factors aid in promoting angiogenesis and neurogenesis. Data from Maleki M, Ghanbarvand F, Behvarz MR, Ejtemaei M, Ghadirkhomi E.[23] Created with BioRender.com.

Peripheral Blood Stem Cells (PBSC)

Blood stem cells are a small number of bone marrow stem cells that have been mobilized into the blood by hematopoietic growth factors, which regulate the differentiation and proliferation of cells. They are increasingly used in cell therapies, most recently for the regeneration of non-hematopoietic tissue, including neurons. Recombinant human granulocyte colony-stimulating factor (G-CSF) has been used as a stimulator of hematopoiesis, which in turn amplifies the yield of peripheral blood stem cells.[27]

Clinical Trial Assessments

The literature review considered 11 clinical trials that satisfied the inclusion criteria. A total of 368 patients were enrolled including 179 patients treated with various types of adult stem cells. The clinical trial number 7 contained a historical control of 59 patients included in the data analysis (Figure 3). The analysis was done on the published clinical and functional outcomes of various tests such as mRS, and mBI. The analysis compared the patients' clinical outcomes post stem cell therapy to the baseline clinical results. The variance in the patient population should be noted.

Meta-analyses were conducted using modified Rankin scale (mRS) and Barthel Index (BI) scores. In the clinical trials, mRS and BI scores are commonly used scales to assess functional outcome in stroke patients. The BI score was developed to measures the patient's performance in 10 activities of daily life from self-care to mobility. An mRS score follows a similar outcome but measures the patients'

independence in daily tasks rather than performance. OpenMeta[Analyst], an open-source meta-analysis software, was used to produce random-effects meta-analyses and create the forest plots. The number of patients, mean, and standard deviation (SD) of the scores were calculated to determine the study weights and create the forest plots.

Comparison of Patient Outcome Between Clinical Trials

All 11 clinical trials were compared based on their clinical and functional outcomes (Table 1; Figure 4). The data shows that stem cell therapy is relatively safe and viable in the treatment of stroke, indicating an improvement in patients' overall health. However, when compared to the control, the improvement is not significant as patients in the control group also exhibited an improved clinical and functional outcome. Across trials that assigned a control group, the patients either received a placebo, or alternative form of treatment including physiotherapy. Variance in functional and clinical tests used to assess patients, and the number of patients enrolled in each trial results in a discrepancy in reporting. Most of the trials failed to report whether the patients suffered from an acute, subacute or chronic stroke which also affects the results of the treatments, with acute and subacute being the optimal periods to receive treatment due to cell plasticity and inhibiting unwarranted inflammation.[39] The deaths in both the treatment and control population were attributed to the progression of the disease and are likely not the result of the treatment. Albeit, it has been noted down as they had occurred during the follow-up period.

A meta-analysis was conducted using modified Rankin scale (mRS) and Barthel Index (BI) scores. The results of the mRS scores were analyzed (Figure 5A; Table 2). In terms of study weights, CT6 is the highest (40.07%) as shown in Table 2. The combined results of the mRS functional test from CT1, CT5, CT6, and CT11 show a non-significant statistical heterogeneity in the studies (p-value 0.113). In conjunction, BI scores were analyzed and a meta-analysis was conducted using four comparable trials (Figure 5B; Table 3). In terms of study weights, CT3 is the highest (32.384%) as shown in Table 3. The combined results of BI scores from CT5, CT3, CT10, and CT11 show a statistical heterogeneity in the results of the studies (p-value 0.004) thus, precision of results is uncertain. More comparable studies are needed to have a better outcome. Therefore, standardized testing in trails should be considered in future trials.

Discussion

Across all trials, patients injected with the MSCs, and other cell types did not trigger a degradation of the patient conditions demonstrating the safety of the procedures. However, the efficacy of the use of adult stem cells is less clear when compared to patients in the control group. This discrepancy could, however, exhibit improvement in patients receiving the treatment compared to the baseline clinical outcomes. However, when therapy results are compared to the patients in the control population that either received a placebo, physiotherapy, or prescribed medication, the efficacy of the use of adult stem cells is less clear.

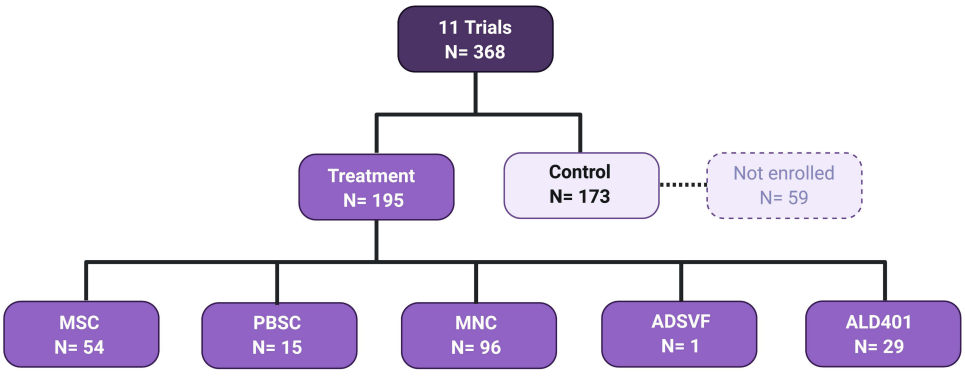

Figure 3 Schematic representing an overview of the total number of patients enrolled in all 11 clinical trials and the number of patients administered with each type of adult stem cell.

Abbreviations: MSC, mesenchymal stem cells; PBSC, peripheral blood stem cells; MNC, mononuclear stem cells; ADSVF, adipose derived stromal vascular fraction; ALD401, aldehyde dehydrogenase-bright stem cells.

Table 1 Overview of Selected Clinical Trials

Trial Code	Reference	Route of Delivery	Cell Type	Number of Cells Injected (Frequency)	Follow-Up Period	Assessment	Number of Patients			Major Outcomes
							Total	Treatment	Control	
CT1	[28]	Intravenous	MSC	$5x10^7$ (two doses)	5 years	MRI, NIHSS, mRS	52	16	36	Improvement in mRS score in treatment arm.
CT2	[29]	Intravenous	MSC	$0.6x10^8$ to $1.6×10^8$ (one dose)	1 year	MRI, NIHSS, mRS	12	12	-	Reduction in lesion volume indicating improvement.
CT3	[30]	Intra-arterial	BMMNC	$1.2x10^6$ to $2.79×10^6$ (One dose)	6 months	FLAIR, MRI, NIHSS, mRS	5	5	-	Improvement in mRS and NIHSS scores. Reduction in lesion volume indicating improvement.
CT4	[31]	Intravenous	MSC (20) and MNC (20)	$5x10^7$ to $6×10^7$ (one dose)	6 months	MRI, MRC, Ashworth, FM, mBI	40	40	-	Improvement in the BI score in treatment arm.
CT5	[32]	Intravenous	BMMNC	~$2.8x10^8$ (one dose)	20 months	BI, NIHSS, mRS	119	59	60	Safe but no beneficial effects.
CT6	[33]	Stereotactic	PBSC	$3x10^6$ to $8×10^6$ (one dose)	1 year	MRI, NIHSS, ESS, EMS, mRS, FNA	30	15	15	Functional and clinical improvement in the treatment arm.
CT7	[34]	Intravenous	BMMNC	$1.9x10^8$ to $2.9×10^8$ (one dose)	6 months	BI, FLAIR, MRI, NIHSS, mRS	12	12	59*	Better clinical outcome at the higher dose.
CT8	[35]	Intra-arterial	BMMNC	Max $5×10^8$ (one dose)	1 year	BI, CT, MRI, NIHSS, mRS	20	10	10	Improvement observed in clinical and functional scores in treatment arm
CT9	[36]	Intraventricular	ADSVF	$4.05x10^5$ to $6.2x10^7$/cc	3 years	MRI	1	1	-	Considered to be safe. Patient remained stable throughout the follow up period.
CT10	[37]	Intracarotid	ALD401	Not mentioned	1 year	MRI, BI, NIHSS, CT, mRS	46	29	17	No difference in mRS scores between treatment and control arm. No significant clinical or functional differences.
CT11	[38]	Intravenous	MSC	Up to $3×10^8$ (two doses)	2 years	BI, fMRI, NIHSS, mRS	31	16	15	Motor skill improvement in the treatment group.

Abbreviations: ADSVF, adipose-derived stromal vascular fraction; ALD-401, aldehyde dehydrogenase 401; BI, Barthel Index; BM-MNC, bone marrow-derived mononuclear cells; CT, computed tomography; EMS, emergency medical service; FLAIR, fluid attenuated inversion recovery; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; MSCs, mesenchymal stem cells; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PBSC, peripheral blood stem cells.

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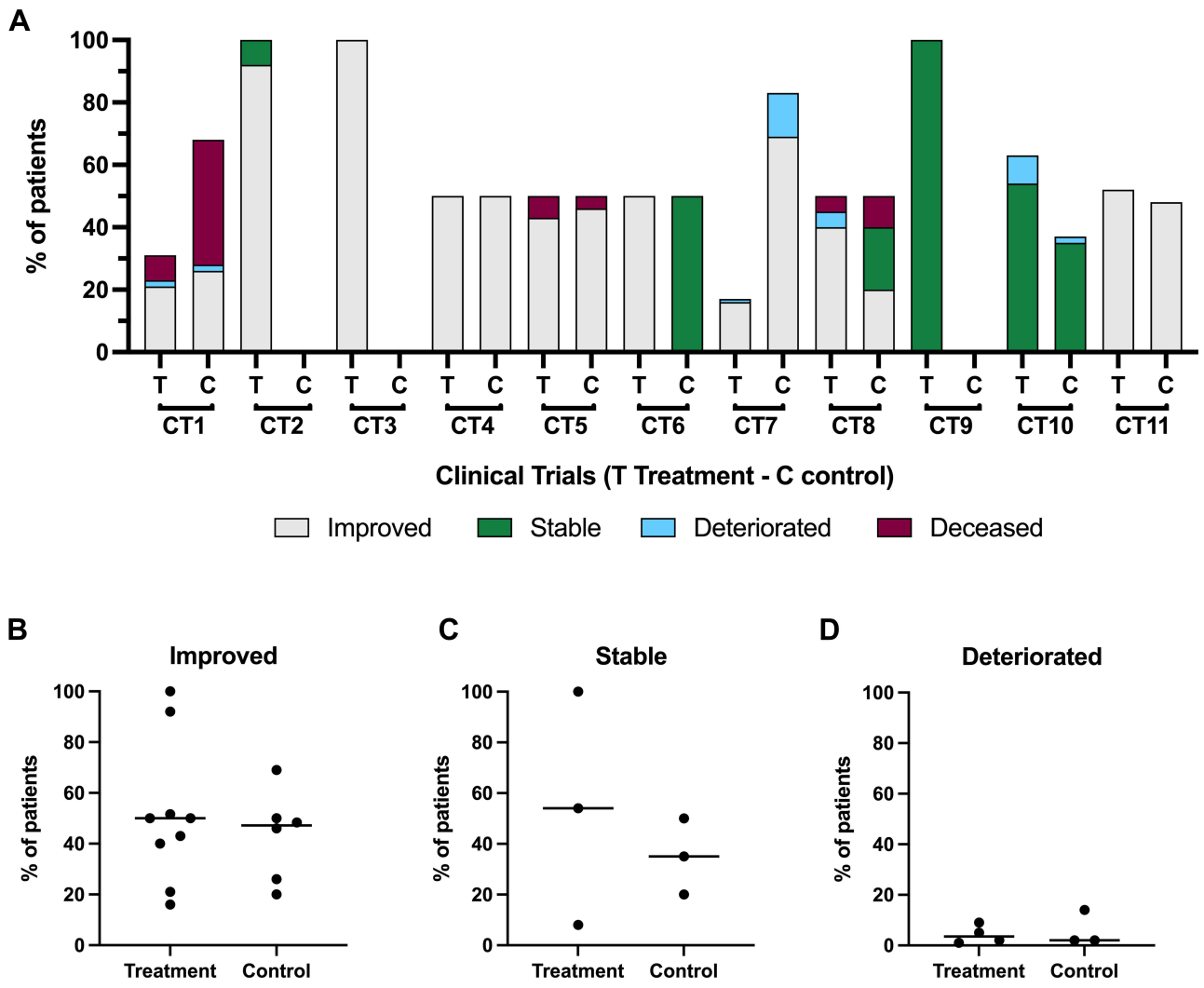

Figure 4 Overview of clinical outcomes of the 11 clinical trials (N=368). (**A**) The chart shows the percentages of patients who have either improved, remained stable, deteriorated, or deceased. Some clinical trials are without a control arm. (**B**) The plot shows the overall percentage of patients that have improved after receiving either the stem cell treatment versus the standard of care. (**C**) The plot shows the overall percentage of patients that have remained stable and showed no clinical or functional improvement in the follow up period. (**D**) The plot shows the overall percentage of the patients whose condition has deteriorated in the follow up period.

Although multiple adult stem cell types have been used, mesenchymal stem cells have been widely used in many clinical trials. Albeit there is a consensus that the therapeutic and clinical outcomes of mesenchymal stem cell treatments are not yet significantly effective compared to the control treatment. Some trials have shown patient improvements, such as CT6 and CT8, where the investigators used PBSCs or BMMNSC, respectively. Although subjectively, the cells appear to be therapeutic, objectively, there are many limitations to the study designs included in this review. Not all the trials enrolled a control arm for a better comparison as some were only testing safety rather than efficacy. Therefore, we cannot conclude whether autologous adult stem cells are an effective therapeutic stroke treatment. Only autologous cells were included in this review as they are non-immunogenic.

Another factor to consider is the evident discrepancy in the number of patients enrolled in each trial. The trials included in this review are in Phase I and II trials, which primarily focus on safety rather than efficacy. Intravenous injection was the most used method of cell delivery due to its convenience and safety. However, it is commonly considered that this approach is not the most effective way of delivery, as the majority of the

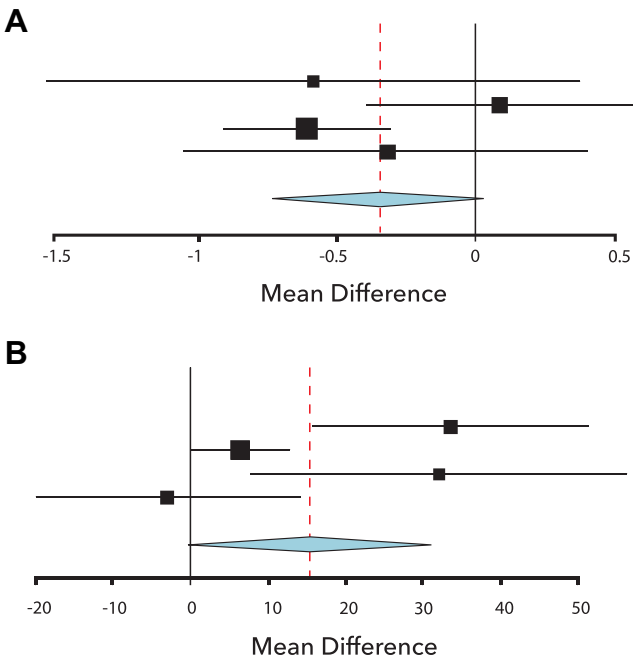

Figure 5 Meta-analysis conducted using three comparable trials. (**A**) Meta-analysis conducted using four comparable trials (CT1, CT5, CT6, CT11) for the mRS test. (**B**) Meta-analysis conducted using four comparable trials (CT3, CT5, CT10, and CT11) for the BI test.

transplanted cells get absorbed by non-targeted organs, and the remaining cells find difficulty passing the blood-brain barrier. Due to this dilemma, the most obvious approach would be to inject the cells directly into the brain. However, a stereotactic procedure is invasive and will require general anesthesia, which may compromise patients' health, especially ones suffering from acute ischemic stroke.[40] Thus, an intra-arterial delivery seems feasible to accomplish the task as it is less invasive and might be more effective than an intravenous treatment such as the cases observed in CT3 and CT8. In CT11, the patients demonstrated a visible fmRI recovery as well as recovery of motor function in patients that have received a stem cell treatment. However, the analysis and test scores show no significance between the treatment group and the control group.

Only a few studies were comparable using a similar evaluation approach. Considering these factors, better study designs enrolling a higher number of patients in randomized clinical trial against the standard of care are needed. Moreover, a better grouping of the patients based on the type and stage of stroke may provide more relevant information for the safety and efficacy of adult stem cells for the recovery and prevention of recurrence of stroke patients.

Table 2 Clinical Outcomes of mRS Test

mRS	Study Weight (%)	Treatment			Control			Mean Diff	Lower Limit	Upper Limit
		Mean	SD	Total	Mean	SD	Total			
CT1	12.387	4.0625	1.48	16	4.6389	1.869	36	−0.5764	−1.524	0.372
CT5	29.208	3.55	1.304	59	3.467	1.308	59	0.083	−0.388	0.554
CT6	40.070	2.1	0.3	15	2.7	0.5	15	−0.6	−0.895	−0.305
CT11	18.335	2.75	0.93	16	3.07	1.1	15	−320	−1.039	0.399
Total	100			106			125			
Heterogeneity p-value	0.113									

Note: Forest plot values of comparable studies.

Table 3 Clinical Outcomes of BI Test

BI	Study Weight (%)	Treatment Mean	SD	Total	Control Mean	SD	Total	Mean Diff	Lower Limit	Upper Limit
CT5	23.930	63.1	29.6	59	63.6	29.6	59	33.5	15.6	51.4
CT3	32.384	74.8	11.5	20	68.4	9.3	20	6.4	−0.82	12.882
CT10	19.133	54	28	24	22	38	12	32	7.757	56.243
CT11	24.553	82	27.83	16	85	20.48	15	−3	−20.128	14.128
Total	100			119			106			
Heterogeneity p-value	0.004									

Note: Forest plot values of comparable studies.

Abbreviations

ADSVF, Adipose-derived stromal vascular fraction; ASCs, Adult stem cells; ALD-401, Aldehyde dehydrogenase 401; BI, Barthel Index; BM-MNC, Bone marrow-derived mononuclear cells; FLAIR, Fluid attenuated inversion recovery; fMRI, Functional magnetic resonance imaging; G-CSF, Granulocyte colony-stimulating factor; MRI, Magnetic resonance imaging; MSCs, Mesenchymal stem cells; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PBSC, Peripheral blood stem cells; SD, Standard deviation; tPA, tissue plasminogen activator.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

We declare there is no conflict of interest.

References

1. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. *Bull World Health Organ*. 2016;94(9):634A–635A. doi:10.2471/BLT.16.181636
2. Donnan G, Fisher M, Maclead M, Davis S. Stroke. *Lancet*. 2008;373(9674):1496. doi:10.1016/S0140-6736(09)60833-3
3. Umut Canbek YB, Imerci A, Akgün U, Yesil M, Aydin A. Characteristics of injuries caused by paragliding accidents: a cross-sectional study. *World J Emerg Med*. 2015;6(1):44–47. doi:10.5847/wjem.j.1920
4. Roth EJ, Heinemann AW, Lovell LL, Harvey RL, McGuire JR, Diaz S. Impairment and disability: their relation during stroke rehabilitation. *Arch Phys Med Rehabil*. 1998;79(3):329–335. doi:10.1016/S0003-9993(98)90015-6
5. Joy MT, Carmichael ST. Encouraging an excitable brain state: mechanisms of brain repair in stroke. *Nat Rev Neurosci*. 2021. doi:10.1038/s41583-020-00396-7
6. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Prog Neurobiol*. 2014;115:157–188. doi:10.1016/j.pneurobio.2013.11.006
7. Fern R, Matute C. Glutamate receptors and white matter stroke. *Neurosci Lett*. 2019;694:86–92. doi:10.1016/j.neulet.2018.11.031
8. Zhao L, Willing A. Progress in neurobiology enhancing endogenous capacity to repair a stroke-damaged brain: an evolving fi eld for stroke research. *Prog Neurobiol*. 2018;163–164:5–26. doi:10.1016/j.pneurobio.2018.01.004

9. Hasan TF, Rabinstein AA, Middlebrooks EH, et al. Diagnosis and management of acute ischemic stroke. *Mayo Clin Proc Themat Rev Neurosci*. 2018;93(4):523–538. doi:10.1016/j.mayocp.2018.02.013
10. Abraham MK, Chang WTW. Subarachnoid hemorrhage. *Emerg Med Clin NA*. 2016;34(4):901–916. doi:10.1016/j.emc.2016.06.011
11. Wei L, Wei ZZ, Jiang MQ, Mohamad O, Yu SP. Stem cell transplantation therapy for multifaceted therapeutic benefits after stroke. *Prog Neurobiol*. 2017. doi:10.1016/j.pneurobio.2017.03.003
12. Biehl JK, Russell B. Introduction to stem cell therapy. *J Cardiovasc Nurs*. 2009;24(2):98–103. doi:10.1097/JCN.0b013e318197a6a5
13. Larijani B, Esfahani EN, Amini P, et al. Stem cell therapy in treatment of different diseases. *Acta Med Iran*. 2012;50(2):79–96.
14. Lo B, Parham L. Ethical issues in stem cell research. *Endocr Rev*. 2009;30(3):204–213. doi:10.1210/er.2008-0031
15. Wagers AJ, Weissman IL. Plasticity of adult stem cells. *Cell*. 2004;116(5):639–648. doi:10.1016/S0092-8674(04)00208-9
16. Fernández-Susavila H, Bugallo-Casal A, Castillo J, Campos F. Adult stem cells and induced pluripotent stem cells for stroke treatment. *Front Neurol*. 2019;10. doi:10.3389/fneur.2019.00908
17. Bang OY. Current status of cell therapies in stroke. *Int J Stem Cells*. 2009;2(1):35–44. doi:10.15283/ijsc.2009.2.1.35
18. Einstein O, Ben-Hur T. The changing face of neural stem cell therapy in neurologic diseases. *Arch Neurol*. 2008;65(4):452–456. doi:10.1001/archneur.65.4.452
19. Dabrowska S, Andrzejewska A, Lukomska B, Janowski M. Neuroinflammation as a target for treatment of stroke using mesenchymal stem cells and extracellular vesicles. *J Neuroinflammation*. 2019;16(1):1–17. doi:10.1186/s12974-019-1571-8
20. Wagenaar N, Nijboer CHA, Van Bel F. Repair of neonatal brain injury: bringing stem cell-based therapy into clinical practice. *Dev Med Child Neurol*. 2017;59(10):997–1003. doi:10.1111/dmcn.13528
21. Secunda R, Vennila R, Mohanashankar AM, Rajasundari M, Jeswanth S, Surendran R. Isolation, expansion and characterisation of mesenchymal stem cells from human bone marrow, adipose tissue, umbilical cord blood and matrix: a comparative study. *Cytotechnology*. 2015;67(5):793–807. doi:10.1007/s10616-014-9718-z
22. Lin CS, Xin ZC, Dai J, Lue TF. Commonly used mesenchymal stem cell markers and tracking labels: limitations and challenges. *Histol Histopathol*. 2013;28(9):1109–1116. doi:10.14670/HH-28.1109
23. Maleki M, Ghanbarvand F, Behvarz MR, Ejtemaei M, Ghadirkhomi E. Comparison of mesenchymal stem cell markers in multiple human adult stem cells. *Int J Stem Cells*. 2014;7(2):118–126. doi:10.15283/ijsc.2014.7.2.118
24. Bhartiya D. Clinical translation of stem cells for regenerative medicine: a comprehensive analysis. *Circ Res*. 2019;124(6):840–842. doi:10.1161/CIRCRESAHA.118.313823
25. Lv W, Li WY, Xu XY, Jiang H, Bang OY. Bone marrow mesenchymal stem cells transplantation promotes the release of endogenous erythropoietin after ischemic stroke. *Neural Regen Res*. 2015;10(8):1265–1270. doi:10.4103/1673-5374.162759
26. Muir T. Peripheral blood mononuclear cells: a brief review origin of peripheral blood mononuclear cells; 2020:1–7.
27. Wang Z, Schuch G, Williams JK, Soker S. Peripheral blood stem cells. *Handb Stem Cells*. 2013;2:573–586. doi:10.1016/B978-0-12-385942-6.00050-0
28. Lee JS, Hong JM, Moon GJ, et al. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke.. *Stem Cells*. 2010;28(6):1099–1106. doi:10.1002/stem.430
29. Honmou O, Houkin K, Matsunaga T, et al. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. *Brain*. 2011;134(6):1790–1807. doi:10.1093/brain/awr063
30. Banerjee S. T ISSUE -S PECIFIC P ROGENITOR AND S TEM C ELLS intra-arterial immunoselected CD34 + stem cells for acute ischemic stroke; 2014.
31. Bhasin A, Padma Srivastava MV, Mohanty S, Bhatia R, Kumaran SS, Bose S. Stem cell therapy: a clinical trial of stroke. *Clin Neurol Neurosurg*. 2013;115(7):1003–1008. doi:10.1016/j.clineuro.2012.10.015
32. Prasad K, Sharma A, Garg A, et al. Intravenous autologous bone marrow mononuclear stem cell therapy for ischemic stroke: a multicentric, randomized trial. *Stroke*. 2014;45(12):3618–3624. doi:10.1161/STROKEAHA.114.007028
33. Chen DC, Lin S-Z, Fan J-R, et al. Intracerebral implantation of autologous peripheral blood stem cells in stroke patients: a randomized Phase II study. *Cell Transplantation*. 2014;23(12):1599–1612. doi:10.3727/096368914X678562
34. Taguchi A, Sakai C, Soma T, et al. Intravenous autologous bone marrow mononuclear cell transplantation for stroke: phase1/2a clinical trial in a homogeneous group of stroke patients. *Stem Cells Dev*. 2015;24(19):2207–2218. doi:10.1089/scd.2015.0160
35. Bhatia V, Gupta V, Khurana D, Sharma RR, Khandelwal N. Randomized assessment of the safety and efficacy of intra-arterial infusion of autologous stem cells in subacute ischemic stroke. *Am J Neuroradiol*. 2018;39(5):899–904. doi:10.3174/ajnr.A5586
36. Duma C, Kopyov O, Kopyov A, et al. Human intracerebroventricular (ICV) injection of autologous, non-engineered, adipose-derived stromal vascular fraction (ADSVF) for neurodegenerative disorders: results of a 3-year Phase 1 study of 113 injections in 31 patients. *Mol Biol Rep*. 2019;46(5):5257–5272. doi:10.1007/s11033-019-04983-5
37. Savitz SI, Yavagal D, Rappard G, et al. A phase 2 randomized, sham-controlled trial of internal carotid artery infusion of autologous bone marrow-derived ALD-401 cells in patients with recent stable ischemic stroke (RECOVER-stroke). *Circulation*. 2019;139(2):192–205. doi:10.1161/CIRCULATIONAHA.117.030659
38. Jaillard A, Hommel M, Moisan A, et al. Autologous mesenchymal stem cells improve motor recovery in subacute ischemic stroke: a randomized clinical trial. *Transl Stroke Res*. 2020;11(5):910–923. doi:10.1007/s12975-020-00787-z
39. Kwak K-A, Kwon H-B, Lee JW, Park Y-S. Current perspectives regarding stem cell-based therapy for ischemic stroke. *Curr Pharm Des*. 2018;24(28):3332–3340. doi:10.2174/1381612824666180604111806
40. Anastasian ZH. Anaesthetic management of the patient with acute ischaemic stroke. *Br J Anaesth*. 2014;113:ii9–ii16. doi:10.1093/bja/aeu372