Original Article

Systematic Review of Experimental Ischemic Stroke Treatment with Neural Stem Cells in Preclinical Studies

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Abstract

Background and Objective: Transplantation of temporary cells is effective in ischemic stroke treatment. In this research, a systematic review and meta-analysis was used to study the biological effect of stem cell treatments in animal models of ischemic stroke.

Material & Method: A search was made in the databases. 83 articles that were related to our study in terms of content and topic and met the inclusion criteria were selected. These studies were selected from articles published between 2000 and 2022. In the initial search, 10538 records were obtained. At this stage, 4088 records were removed due to duplication and all articles that did not meet the inclusion criteria or were inappropriate due to indirect connection with the subject (858 records). Then 773 articles were retrieved for full text review. A thorough review resulted in the final selection of 27 studies.

Result: The results showed that the performance (sensory-motor, neurological or behavioral) improved in 83.13%, infarct volume decreased in 39.75%, increased angiogenesis and vessel density in 18%, decreased number of microglial cells in 14.45%. And there was a decrease in the amount of apoptosis in 8.43% of the studies.

Conclusion: Stem cell therapy can improve neural function defects and infarct volume and exert a potential neuroprotective effect for experimental ischemic stroke.

Keywords: Stem cell-based Therapy, Ischemic Stroke, Infarction, Neurological Function, Preclinical Systematic Review.

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INTRODUCTION

A stroke occurs as a result of cerebral blood supply disruption for 24 hours or until death and subsequent disruption of nervous system (1). This complication is one of the main causes of death and severe disability worldwide (2, 3). In general, there are two types of ischemic stroke and hemorrhagic stroke (4). In hemorrhagic stroke, intracerebral bleeding and subarachnoid bleeding occur (4). While ischemic stroke is a heterogeneous disease and many underlying pathological processes play a role in it (5). This type of stroke occurs when a blood vessel in the neck or brain is blocked, resulting in reduced blood flow in the brain (6, 7). About 85% of strokes are ischemic, and in most of these strokes, the mechanism is known, and its main causes include atherosclerotic, cardiogenic, and lacunar mechanisms (5). Since stroke has a wide impact on patients' lives and financial costs, many efforts have been made to improve and treat it (3 and 8). Although the incidence of this complication is high, there are limited clinical treatments for it, which include endovascular mechanical therapy (thrombectomy) and intravenous thrombolysis by tissue plasminogen activator (tPA) (8). However, due to the length of these treatment methods, many patients could not receive the necessary treatment and suffered lifelong disabilities (9). Therefore, new methods are needed to minimize the harmful effects and improve the treatment outcome (8). Stem cell transplantation is one of the promising treatments in ischemic stroke treatment (2). Recent advances in stem cell research indicate that endogenous and exogenous neural stem cells (NSCs) can provide promising therapies (10). Transplanted NSCs have the ability to differentiate into functional brain neurons and can also reduce the toxic microenvironment by delivering neurotrophic factors and protect the host cells (Hamblin and Chen). Due to the importance of these cells in the treatment of ischemic stroke, the present study deals with the systematic investigation of the treatment of this condition with neural stem cells in preclinical studies.

MATERIALS AND METHOD

Search strategy and study selection

Research articles published in English were analyzed using relevant terms in PubMed, Web of Science Core, EMBASE, Scopus, CINAHL, PsycINFO, International Bibliography of Social Science and DoPHER databases. Initially, one person generated the terms required for search, and then these terms were reviewed by all authors. Search terms for screening articles included "stem cell", "stroke", "ischemic", "therapy", "preclinical", "cell-based therapy". The combination of these words with the operators "and" and "or" was also examined. The English equivalent of all these words was also searched. There was no time limit for the search and all articles related to the topic were reviewed.

Inclusion and exclusion criteria

The inclusion criteria included all articles in which one of the following items was examined:

Articles in which focal ischemic stroke, caused by transient middle cerebral artery occlusion (MCAO) or permanent MCAO, were examined without restrictions on animal species as well as gender, age, weight and sample size. Controlled studies in which control group (receive drug, saline, positive control drug or no treatment) and experimental group (receiver of allogeneic stem cells or autologous) with no restrictions on dose, mode and time of primary treatment were investigated. Studies in which both NFS and infarct size/infarct volume were measured.

The exclusion criteria were as follows:

Uncontrolled studies that lacked a control group. Studies in which the non-focal cerebral ischemia model, such as the global cerebral ischemia model, hypoxic-ischemic models or traumatic models were investigated. Articles whose full text was not available. Also, data related to review studies and articles that were not original were not extracted.

Data screening and extraction

Two trained authors performed the search strategies and then they separately screened the titles and abstracts of the articles and selected the relevant studies based on their relevance to the objectives of the review article, inclusion and exclusion criteria, and their quality. The abstract of all articles was reviewed and in cases where the article could not be removed based on the title or abstract, the full text of the article was retrieved and evaluated. In case of discrepancy, two researchers reviewed the article completely and reached a consensus and mentioned the reasons for including or removing the article.

In initial search, 10538 records were obtained. At this stage, 4088 records were removed due to duplication and all articles that did not meet inclusion criteria or were inappropriate due to indirect connection with the subject (858 records). Then 773 articles were retrieved for full text review. A thorough review resulted in the final selection of 83 studies that met all inclusion criteria. The method of presenting topics, including analysis and interpretation, determining the purpose of the study and gathering findings was based on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Figure 1).

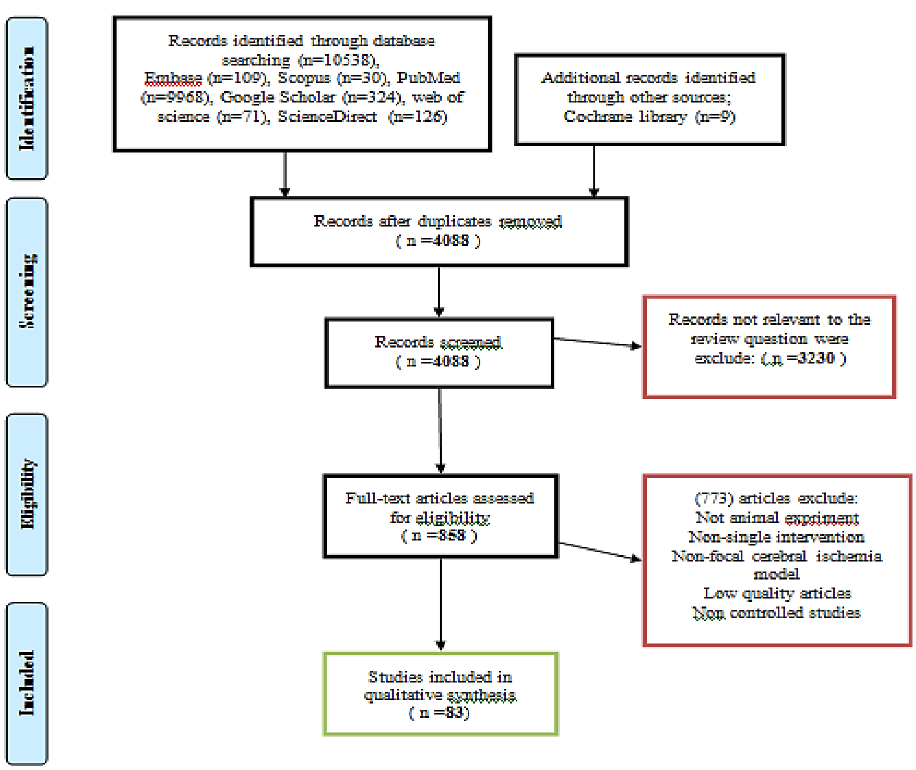

Figure 1: Reviewed articles Selection diagram

RESULTS AND DISCUSSION

Based on inclusion criteria, a number of 83 studies were separated and examined more closely, and their results are shown in Table 1. Based on data extracted from Table 1, the highest frequency of stem cells used in research related to BMSCs (24%), MSCs (16.86%), NSCs (15.66%), ADMSCs (12%) and huc -MSCs (6%). Other cells include ESCs, iPS, hucB-MSCs, hipc-MScs, DPSCs, Wj-MSCs, hAFSCs, ghMSCs, and LIF-NSCs. Also, the data of this table shows that the improvement of function (sensory-motor, neurological or behavioral) in 83.13%, reduction of infarct volume in 39.75%, increase in angiogenesis and vessel density in 18%, decrease in the number of microglial cells in 14.45%. % and there was a decrease in the amount of apoptosis in 43.8% of the studies.

	Authors and year	Therapy groups	Results
1	Zhao et al, 2002 (11)	Using human MSCs	Significant improvement of performance, under the influence of proteins secreted by transplanted mesenchymal stem cells
2	Zhang et al, 2006 (12)	Using bone marrow stromal cells (BMSCs)	Significant performance improvement compared to control group Increase in number of 5-Bromo-2-deoxyuridine and Ki67 positive cells in subventricular zone Increased differentiation of proliferated astrocyte cells increased bone morphogenetic protein 2/4, connexin-43 and synaptophysin expression in ischemic border area
3	Shen et al, 2007 (13)	Using bone marrow stromal cells (BMSCs)	Significant recovery in behavior of treated mice Astrocyte expression, glial fibrillary acidic protein, and neuronal marker, microtubule-associated protein-2 Reducing scar thickness and increasing the number of proliferating cells and oligodendrocyte progenitor cells along the subventricular zone
4	Andrews et al, 2008 (14)	Adult human bone marrow-derived somatic cells (hABM-SC)	Improvement of forelimb function in hABM-SC treatment due to increased structural neuroplasticity of damaged brain areas
5	Koh et al, 2008 (15)	Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs)	Improvement of neurobehavioral function and reduction of infarct volume after transplantation of mesenchymal stem cells hUC-MSC Increased nestin expression in the hippocampus in the group implanted with hUC-MSC compared to the control group
6	Kamiya et al, 2008 (16)	Using bone marrow mononuclear cells (BMMCs) (through the carotid artery) (group IA) or femoral vein (group IV) or vehicle	Reduction of total infarct volume in group IA, but no reduction in group IV Greater number of PKH26 positive cells in group IA compared to group IV Improved motor performance in the IA group compared to the vehicle group
7	Li et al, 2008 (17)	Investigating the effect of mesenchymal stem cell passage on their effects in mouse stroke model	More pronounced behavioral recovery and neurogenesis in mice with later-passage human MSCs compared to mice with previous-passage human MSCs Increased expression of tissue levels of trophic factors, including glial cell line-derived neurotrophic factor, nerve growth factor, vascular endothelial growth factor, and hepatocyte growth factor
8	Liao et al, 2009 (18)	Use of Human Umbilical Cord Multipotent Mesenchymal Stromal Cells (UC-MSC)	Significant reduction of injury volume and neurological functional deficits by UC-MSC treatment compared to phosphate buffered saline control. UC-MSC differentiated extensively into endothelial cells Increased vascular density and vascular endothelial growth factor and expression of basic fibroblast growth factor
9	Liu et al, 2009 (19)	Using bone marrow-derived mesenchymal stem cells (MSCs) transplantation Operation group, MCAO group, vehicle group and group treated with MCAO +	Significant performance improvement compared to controls by MSCs 14 days after transplantation mRNA expression of IL-10 and its protein level in MSC group compared to MCAO group and vehicle group

		.MSCs	Decreased expression of TNF-α on day 4 after MCAO in MSC group compared to MCAO group and vehicle group Reduction of infarct volume by transplantation with mesenchymal stem cells on days 1 and 4
10	Wu et al, 2008 (20)	Injection of GFP-labeled BMSCs into mice	Reduction of scar size, limited apoptosis and increased expression of angiogenic factor and vascular density in ischemic area compared to control group, as well as significant improvement in nerve severity scores.
11	Hicks et al, 2009 (21)	Transplantation of neural progenitor cells derived from human embryonic stem cells (hESC) or vehicle	No effect on rehabilitation and reduction of cerebral cortex infarct volume or hNPC transplantation Improvement in sensorimotor function after dMCAO by hESC-derived neural progenitor grafts, but failure to restore more complex sensorimotor functions by them
12	Stroemer et al, 2009 (22)	Using vehicle or CTX0E03 cells for mice	Significant recovery of sensorimotor dysfunction in CTX0E03 cell implanted groups compared to vehicle group Improvement in function and differentiation of surviving CTX0E03 cells into oligodendroglial and endothelial phenotypes
13	Jin et al, 2010 (23)	NPCs derived from human embryonic stem cells (hESC) combined with biological materials (Matrigel)	Improvement of infarct volume and performance on cylinder and upper body swing tests with transplantation Higher infarct formation by aged rats
14	Kawai et al, 2010 (24)	Using induced pluripotent stem (iPS) Sham group + PBS (phosphate buffered saline), middle cerebral artery occlusion (MCAO) + PBS group), Sham + iPS group and MCAO + iPS group	Expansion of transplanted iPS cells and formation of larger tumors in brain after ischemia Delayed clinical improvement of MCAO + iPS group compared to MCAO + PBS (phosphate buffered saline) group
15	Leu et al, 2010 (25)	IS group and 1 ml of intravenous saline IS group and intravenous ADMSCs	Greater BIA in the control group compared to treatment group Left turn movement with a higher frequency in control group than in treatment group Increased mRNA expression of Bax, caspase 3, interleukin (IL)-18, toll-like receptor 4 and plasminogen activator inhibitor-1 Higher cell proliferation and lower number of small vessels The prevalence of glial acid fibrillary protein in control group compared to the treatment group
16	Shen et al, 2010 (26)	NSCs treatment group, MCAO vehicle group and a sham group	Improvement of the behavior of ischemic rats and the localization of transplanted cells in damaged areas by MCAO Reduction of infarct volume and brain atrophy after transplanted NSCs treatment Suppression of expression of inflammatory molecular protein levels by treatment of transplanted NSCs
17	ZHANG et al, 2011 (27)	NSCs group with 17β-estradiol (CE) NSCs group without 17β-estradiol (CN) and control group	Improvement of neurological defects, reduction of morphological changes and reduction of total infarct volume in CN and CE groups There was no significant difference in the expression of fibrillary nestin and glial acidic protein between CN and CE groups at all times.
18	Bao et al, 2011 (28)	Human bone marrow-derived mesenchymal stem cells (hBMSCs)	Significant improvement of behavior in mice treated with hBMSCs at 14 days after MCAO Identification of higher levels of brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and vascular endothelial growth factor (VEGF) in brains of mice treated with hBMSCs Improving performance after ischemia in rats
19	Gutiérrez-Fernández et al, 2011 (29)	The use of bone marrow-derived mesenchymal stem cells (MSCs) in two ways i.v. or intracarotid (i.c.)	Neurological recovery in treated groups The presence of the highest cytokine levels in the i.v. group. MSCs and i.c. Control No reduction in infarct volume in any of the treatments

			Increased number of BrdU cells at 14 days in periinfarct area Higher expression of VEGF in i.c. MSCs control group Higher number of blood vessels in treated groups
20	Jiang et al, 2011 (30)	Using human induced pluripotent stem cells (iPSCs)	Migration of transplanted iPSCs into injury areas and their successful differentiation into neuron-like cells Improvement of mice sensorimotor performance after 4 to 16 days of iPSCs transplantation
21	Lim et al, 2011 (31)	Use of hUCB-MSCs	The higher number of migrated cells in ischemic area in intrathecal injection compared to intravenous injection Improving motor function and reducing ischemic damage and better neurological recovery Significant reduction of ischemic damage in intrathecal administration compared to intravenous treatment
22	Liu et al, 2011 (32)	Control group with intravenous injection of 500 microliters of phosphate buffered saline (PBS) without cells GFP group or SVV group with the same volume solution with three million GFP-MSCs or SVV/GFP-MSCs	Increasing the secretion of VEGF and bFGF in hypoxic conditions by modification with SVV in vitro Upregulation of VEGF and bFGF expression in ischemic tissue by modification with SVV Greater survival of transplanted cells in SVV group compared to GFP group at 4 days after transplantation (1.3 times) and at 14 days after transplantation (3.4 times) Reduction of cerebral infarct volume in correction with SVV up to 5.2% in 4 days after stroke and improvement of neurological function after stroke in 14 days after transplantation.
23	Mora-Lee et al, 2012 (33)	Using human multipotent adult progenitor cells (hMAPCs) and human mesenchymal stem cells (hMSCs)	Significant reduction in brain tissue loss in hMSC and hMAPC transplanted animals compared to PBS treated animals Increasing angiogenesis, reducing inflammation and inhibiting glial scar
24	Gutiérrez-Fernández et al, 2013 (34)	Acute intravenous (I.V.) injection of allogeneic bone marrow (BM-MSC) and adipose-derived stem cells (AD-MSC)	Significant improvement in performance at 24 hours after intravenous injection No reduction in infarct volume or any migration in damaged brain cells was observed under the influence of BM-MSC or AD-MSC administration Decreased cell death and increased cell proliferation in both treatment groups Significant increase in vascular endothelial growth factor (VEGF), synaptophysin (SYP), oligodendrocyte (Olig-2) and neurofilament (NF) levels at 14 days after MSC administration
25	Jensen et al, 2013 (35)	Using human induced pluripotent stem cells (iPSCs) or vehicle	The presence of transplanted cells in 8 of the transplanted mice (80%) Expression of NSC markers in 5 rats (63%), neurons in all 8 rats (100%), rare astrocytes in 4 rats (50%) and signs of proliferation in 4 rats (50%) Similarity of stroke volume and behavioral improvement between groups
26	Wang et al, 2013 (36)	Treatment group with iPSC (Induced Pluripotent Stem Cells) Treatment group with ESC (Embryonic Stem Cells) Phosphate buffered saline (PBS) injection control group	Observation of FDG accumulation in ipsilateral cerebral infarction in both iPSC and ESC treatment groups compared to 4-week PBS injection group Significant improvement in glucose metabolism in ESC treatment group in weeks 1 and 2 after stem cell transplantation and then its gradual decrease Performance improvement in both groups treated with stem cells significantly compared to the PBS group (decreased neurological score)
27	Wang et al, 2013 (37)	Using mesenchymal stem cells (MSCs)	Decreased number of ED1 positive macrophage/microglia Decrease in percentage of NF-jB-positive, CD40-positive and TLR2-positive cells in ED1-positive macrophage/microglia
28	Du et al,	Using adipose-derived stem cells (ADSCs)	The effectiveness of using an equal dose of ADSCs

	2014 (38)		intravenously in improving neurological outcome and reducing infarct volume after ischemic brain injury in a long time compared to intra-arterial and intra-ventricular use. Increase in expression level of BDNF, VEGF, bFGF, Bcl-2, IL-10 and decrease in levels of caspase-3 and TNF- in intraventricular and intraarterial groups at 1-7 days after transplantation
29	Huang et al, 2014 (39)	Using human neural stem cells (hNSCs)	Extensive migration of transplanted hNSCs into lesion within 24 h Decreased infarct volume compared to control group Improvement of behavioral defects Decreased microglial activation, decreased expression of proinflammatory factors (tumor necrosis factor-α, interleukin (IL)-6, IL-1β, monocyte chemotactic protein-1, macrophage inflammatory protein-1α) and adhesion molecules (intercellular adhesion molecule- 1, vascular cell adhesion molecule-1), and improving blood-brain barrier damage.
30	Mitkari et al, 2014 (40)	Human bone marrow-derived mesenchymal cells (BMMSC)	A significant increase in the number of blood vessels in the peripheral cortex in MCAO rats treated with BMMSC cells on postoperative day 7 Failure to observe improvement in behavior and performance
31	Cheng et al, 2015 (41)	Use of Neural Stem Cells (NSCs)	Better performance in intravenous infusion of NSCs after middle cerebral artery occlusion (MCAO) No difference in cerebral infarct volume at 7 days after MCAO compared to control Differentiation of NSCs into neurons or astrocytes after MCAO
32	Eckert et al, 2015 (42)	pluripotent stem cell-derived neural stem cells (hiPSC-NSCs)	Migration of HiPSC-NSCs into the stroke lesion within 48 hours after stroke and improvement of neural function Decreased expression of proinflammatory factors (tumor necrosis factor-a, interleukin 6 [IL-6], IL-1b, monocyte chemotactic protein 1, macrophage inflammatory protein 1a), microglial activation
33	Gutiérrez-Fernández et al, 2015 (43)	Acute intravenous injection (I.V.) of hAD-MSCs (human AD-MSCs) or rAD-MSCs (Rat adipose tissue-derived-mesenchymal stem cells)	Significant improvement at 24 hours compared to control group Absence of reduction in lesion size or migration/implantation of cells in the damaged brain Decreased cell death compared to the control group in both groups Higher levels of VEGF and SYP and lower levels of GFAP in the treated groups
34	Hosseini et al, 2015 (44)	Use of neural stem cells (NSCs) and mesenchymal stem cells (MSCs)	Better improvement in neurological scores Reducing size of lesion in brain Lower caspase-3 activity in groups receiving stem cells compared to control group
35	Hosseini et al, 2015 (45)	The use of mesenchymal stem cells from adult mice bone marrow and neural stem cells from ganglionic eminence of 14-day-old rat embryos.	Better neurological examination and fewer brain lesions in the group receiving combined cell therapy The lowest caspase 3 activity in the combined cell therapy group
36	Hosseini et al, 2015 (46)	Using mesenchymal stem cells (MSCs)	Improved optimal neurological function, lowest degree of ischemic brain damage, highest number of bone marrow Mesenchymal stem cell migration to peri-ischemic area and the lowest caspase 3 activity, 12 hours after cerebral ischemia.
37	Li et al, 2015 (47)	Bone marrow mononuclear cells (BMMNCs) from 5-fluorouracil (5-FU)-treated rats (called BMRMNCs)	Reduction of infarct volume, improvement of neural function and more viable cells in the hippocampus under the influence of BMRMNCs Protection against ischemic stroke through increased

			secretion of growth factors and migration to the injured site by BMRMNCs
38	Ma et al, 2015 (48)	The use of neural stem cell transplantation	Significant reduction (16.32%) in cortical infarction in NSC group compared to vehicle Improvement of neural function with neural stem cell transplantation compared to vehicle
39	Otero-Ortega et al, 2015 (49)	Use of adipose-derived mesenchymal stem cells (ADMSC)	Failure to observe ADMSC migration and engraftment after administration The presence of smaller functional defects, smaller lesion area, less cell death, more oligodendrocyte proliferation, more white matter connectivity and more myelin formation in the treatment group.
40	Park et al, 2015 (50)	Using human umbilical cord blood mesenchymal stem cells (hUCB-MSCs)	Better neurobehavioral performance of mice suffering from ischemic stroke treated with mesenchymal stem cells hUCB-MSC compared to control group injected with vehicle Accumulation of neural progenitor cells, angiogenesis and tissue repair factors in ischemic border area under hUCB-MSC transplantation influence.
41	Wang et al, 2015 (51)	Using Galectin-1-secreting neural stem cells (s-NSC)	Reduction of infarct volume in s-NSC transplantation Improved sensory-motor, cognitive functions and stronger neuroprotection than non-engineered NSCs or gal-1 overexpressing (but non-secretory) NSCs Improvement of white matter damage was also observed in stroke rats treated with s-NSC Modulation of microglial function by decreasing secretion of pro-inflammatory cytokines (TNF-a and nitric oxide) in response to LPS stimulation and increasing production of anti-inflammatory cytokines (IL-10 and TGF-b). Decreased expression of CD16 and increased expression of CD206 by Gal-1
42	Wu et al, 2015 (52)	injection of hPDMC (human placenta-derived multi potent stem cells) or vehicle injection of hPDMC (human placenta-derived multi potent stem cells) or vehicle	Behavioral improvement and significant reduction in lesion volume in stroke animals receiving hPDMCs Attenuation of microglia activation by grafts Reduction of cortical lesions and behavioral deficits in adult stroke rats by hPDMC transplantation
43	YANG et al, 2015 (53)	Bone marrow stromal cells (BMSCs)	Significant motor scores in mice after BMSC injection within 1-2 weeks Increased numbers of new vessels, neurofibrils and anastomosed vessels in the infarcted area
44	Bacigaluppi et al, 2016 (54)	neural precursor cells (NPC)	Long-term functional improvement up to 60 days after ischemia by reducing CST degeneration, axonal and dendritic regrowth Dependence of GLT-1 increase caused by transplanted NPCs on VEGF secretion by NPCs Long-term behavioral improvement in NPC-treated mice
45	Choi et al, 2016 (55)	BM-MSCs transplantation in mice	There is a relationship between the amount of behavioral disorder and the volume of cerebral infarction Promotion of neural differentiation and behavioral function by BM-MSCs transplantation
46	Hou et al, 2016 (56)	neural stem cells (NSCs)	Improving the performance of neurobehavioral tests Reducing brain damage caused by stroke Differentiation of transplanted NSCs into neurons and astrocytes
47	Moisan et al, 2016 (57)	Group treated with human BM-MSCs (hBM-MSCs) PBS treated group	Increased vascular density in ischemic area 2 and 3 weeks after hBM-MSC injection Overexpression of angiogenic factors such as Ang1 and transforming growth factor-b1 (TGF-b1) at D16 in hBM-MSC-treated MCAo mice compared with PBS-treated MCAo mice Providing functional benefits and increasing cerebral

			angiogenesis in stroke lesion in delayed IV injection of hBM-MSCs and improving function after stroke
48	Ryu et al, 2016 (58)	hNSC	Improving behavioral performance and reducing cerebral infarction volume The number of proliferating endothelial cells with positive 5-bromo-2'-deoxyuridine factor/anti-von Willebrand factor in ischemic border area of mice treated with human neural stem cells compared to control group Increasing the proliferation of endogenous neural stem cells and their differentiation into mature neural-like cells and increasing angiogenesis
49	Abd El Motteleb et al, 2017 (59)	Using human Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) and Levetiracetam (LEV)	Improvement of memory and learning by mesenchymal stem cells and LEV Significant reduction in infarct size in both treatment groups A significant decrease in expression of glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), phosphatidylethanolamine binding protein 1 (PEBP1) and copper and zinc SOD (Cu/ZnSOD) genes a significant increase in the iNOS prooxidant gene Better results in mice treated with WJ-MSCs compared to mice treated with LEV
50	Lin et al, 2017 (60)	Injection of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) into mice	Increase in the number of ionized calcium adapter molecule 1 (Iba-1) positive cells and the number of Iba-1 positive hypertrophic cells in cerebral ischemic regions two weeks after transient middle cerebral artery occlusion (MCAO) Decrease in number of migratory neuroblasts in cortex, subventricular zone and hippocampus of ischemic brain, followed by a decrease in neurological damage (including brain and nerve infarction) Decrease in the number of hypertrophic microglia/macrophages and increase in the number of newborn neurons
51	Park et al, 2017 (61)	Using human umbilical cord blood mesenchymal stem cells (hUCB-MSCs)	Significant reduction of infarcted brain volume and increase of neurons and vessels in single and repeated hUCB-MSC treatments compared to the control group
52	Souza et al, 2017 (62)	Saline treatment group (control) group treated with minocycline BMMC-transplanted treatment group	Reduction of the number of ED1+ cells in BMMC transplantation and minocycline Preservation of neurons in both treatments compared to control A greater reduction in the number of apoptotic cells in BMMC transplantation (13/1) compared to control treatment (26/5) and minocycline (19/7) Improved performance in both treatments improved recovery in ischemic animals BMMC transplantation (133/8) is more effective in modulating microglial activation and reducing apoptotic cell death than minocycline (244/6) and control (276/3).
53	Yamashita et al, 2017 (63)	iNSC-treated group	Improved survival of stroke model mice with significant functional improvement using transplantation iNSC Improved survival of stroke model mice with significant functional improvement using transplantation iNSC
54	Zhang et al, 2017 (64)	Using NSCs modified with bFGF gene or vehicle (intravenously)	Improved survival, migration, proliferation and differentiation of modified C17.2 cells Improved performance compared to control in intravenous infusion of NSCs and C17.2 cells modified with bFGF gene bFGF promotion of growth, survival and differentiation of C17.2 cells into mature neurons in the infarct region
55	Bi et al, 2018 (65)	Bone marrow mesenchymal stem cells (MH) mild hypothermia(BMSCs)	Significant reduction of mNSS score and percentage of infarct area in combined treatment

			Increased expression of GFAP and VEGF in combined treatment group (on day 5, day 10 after transplantation, respectively; compared to single treatment groups Improve performance by improving angiogenesis
56	Cheng et al, 2018 (66)	mesenchymal stem cell	Reducing infarct volume and improving behavioral performance Decreased inflammatory cytokines IL-1β, IL-6, and TNF-α, and IgG leakage, tight junction protein loss
57	Chi et al, 2018 (67)	adipose-derived mesenchymal stem (ADMSCs) cells	Reduction of neurological severity score by administration of ADMSCs Limitation of brain infarct area as well as cell apoptosis Reducing the expression of IL-1b, IL-6 and TNF-a and suppressing inflammation in the brain.
58	He et al, 2018 (68)	Bone marrow mesenchymal stem cells (BMSCs)	Improves behavior, reduces brain infarct volume and reduces the number of apoptotic cells in rats exposed to cerebral I/R injury by BMSCs transplantation Decreased expression of autophagy-related proteins light chain 3 (LC3)-associated protein 1 and microtubule-associated Beclin-1
59	Huang et al, 2018 (69)	و (MSCs) Mesenchymal stromal cells CCL2	Significantly increased migration of MSCCCR2 into ischemic lesions and improved neurologic outcomes Lower brain edema and blood brain barrier (BBB) leakage level in mice treated with MSCCCR2 compared to MSCd tomato group.
60	Ryu et al, 2018 (70)	Using a transplanted cell sheet or using a vehicle	Improved behavior in cell sheet group due to a significant increase in functional angiogenesis and neurogenesis compared to vehicle group Identification of transplanted cells as pericytes in newly formed perivascular walls The presence of newly formed blood vessels within the cell sheet that was anastomosed to blood vessels of host brain
61	Sowa et al, 2018 (71)	Using dental pulp stem cells (Dental pulp stem cells, DPSC)	Reduction of infarct volume at 3 and 7 days by DPSCs overexpressing HGF Improvement of locomotor performance using unmodified DPSCs and DPSCs overexpressing HGF compared with vehicle administration at 7 days after arterial occlusion Inhibition of microglial activation and proinflammatory cytokine production by DPSCs overexpressing HGF. An increase in the density of small vessels in the areas around the infarct
62	Yamaguchi et al, 2018 (72)	Two groups of young and old cells Using young and old human mesenchymal stem cells (hMSC) in mice	The presence of less microglia and more vessels covered with pericytes in mice treated with young hMSC (9.30) compared to old hMSC (15.29) Improved performance in transplantation with young hMSC (4) via anti-inflammatory effects, vascular maturation and potentially neurogenesis compared to aged hMSC (5)
63	Yu et al, 2018 (73)	Use of allo- or auto-ADMSCs from mice	Lower immunogenicity in auto-ADMSCs compared to allo-ADMSCs Increasing the expression of interleukin-2 and interferon gamma proteins as well as the local accumulation of CD4+ T lymphocytes, CD8+ T lymphocytes and microglial cells by Allo-ADMSC Higher survival rate, longer survival time, wider migration range and less apoptotic cells in Allo-ADMSC treatment Improved performance and greater reduction in infarct volume in auto-ADMSC than allo-ADMSC
64	Zhang et al, 2018 (74)	Bone marrow mesenchymal stem cells (BMSCs)	Improvement of further neural functions in BMSC transplantation via intra-arterial, intravenous and intracerebral routes Increased expression of SYN and Ki-67 and decreased expression of Nogo-A in the brain

65	Zhao et al, 2018 (75)	mild و Adipose-derived stem cell therapeutic hypothermia	Improvement of neurological deficits and reduction of infarct size in combined treatment compared to treatments alone Decrease in the number of TUNEL-positive cells and expression of glial fibrillary acidic protein and increase in the level of vascular endothelial growth factor
66	Cherkashov et al, 2019 (76)	The use of placental mesenchymal stromal cells and neural progenitor cells derived from human induced pluripotent cells	Increasing the survival of animals in the most acute period Accelerating the compensation of neurological deficits Body weight recovery Neural progenitor cells are more effective than human placenta mesenchymal stromal cells
67	Sibov et al, 2019 (77)	Injection of human amniotic fluid-derived stem cells (hAFSCs) into mice	Migration of transplanted cells to the ischemic focus, reduction of infarct volume and improved motor deficits in animal model of stroke
68	Son et al, 2019 (78)	Glia-Like Cells from Late-Passage Human (ghMSC) MSCs	Protection of neurons and brain, regeneration and infarct-damaged brain by ghMSC Positive effect of insulin-like growth factor protein-4 (IGFBP-4) on the beneficial effect of ghMSCs
69	Tian et al, 2019 (79)	(LIF-NSCs) LIFtransfected NSCs	Reduction of infarct volume and neurological recovery by treatment with LIF-NSC Improving regeneration of glial cells and white matter damage
70	Vats et al, 2019 (80)	Use of intra-arterial stem cells (IA)	Improving functional outcome and stress parameters Decreased expression of ASIC1a and inflammations in the cerebral cortex
71	Vahidinia et al, 2019 (81)	(MSCs) Mesenchymal stem cells	Reduction of infarct volume and improvement of behavioral scores 24 hours and 72 hours after tMCAO Decreased neuronal apoptosis and astroglial activity Reduction of JNK phosphorylation after treatment with mesenchymal stem cells
72	XIE et al, 2019 (82)	Using human bone marrow-derived mesenchymal stromal cells (hBMSCs)	Decreased expression of nSS, mRNA and nestin protein in weeks 1, 2, 4 and 8 Increased mRNA and protein expression of Neun, β-III-Tub and GFAP Neural cell formation and increased neural function treated with hBMSc transplantation
73	Chen et al, 2020 (83)	Group 1 (control under sham operation), Group 2 (IS), Group 3 IS+EPCs (injection 3 hours after IS), Group 4 IS+EPCs (prescription after 3 IS days), Group 5 IS+EPCs (administration after IS day 7), group 6 IS+EPCs (administration after IS day 14) and group 7 IS+EPCs (administration after IS -28 day)	The lowest cerebral infarction volume in group 1 and the highest in group 2 The highest protein and cellular levels of inflammation and protein levels of oxidative stress, autophagy and apoptosis in group 2 and the lowest in group 1
74	Oh et al, 2020 (84)	Group transplanted with ep-iPSCNPCs groups transplanted with fibroblast and vehicle (control)	Functional improvements in behavioral and electrophysiological tests in ep-iPSC-NPC transplanted animals Promotion of endogenous brain repair by increasing subventricular zone neurogenesis, and reducing post-stroke inflammation and glial scar formation by transplanted cells.
75	Tobin et al, 2020 (85)	Using interferon-γ–activated mesenchymal stem cells (aMSCγ)	Significant reduction in infarct size and inhibition of microglial activation Recruitment and differentiation of oligodendrocyte progenitor cells into myelin-producing oligodendrocytes in vivo under the influence of aMSCγ treatment
76	Zhang et al, 2020 (86)	Injection of neural stem/progenitor cells (NSPCs) along with artesunate	Improving performance, reducing infarct volume and increasing Nestin expression Inhibiting the transcriptional function of FOXO-3a by inducing its phosphorylation and subsequently reducing p27kip1 and increasing the proliferation of neural stem cells in infarcted cortex through PI3K/AKT signaling and

			reducing ischemia-stroic damage by ART
77	Salehi et al, 2020 (87)	EPI-) epidermal neural crest stem cells bone marrow mesenchymal با (NCSCs (BM-MSCs) stem cells	Better performance in both EPI-NCSCs transplantation (intravenous and intra-arterial) and BMMSCs transplantation (only intra-arterial) compared to MCAO group Reduction of infarct volume ratio in intra-arterial NCSC, intravenous NCSC and intra-arterial MSC groups compared to control group Interventions leading to higher expression levels of Bdnf, nestin, Sox10, doublecortin, β-III tubulin, Gfap and interleukin-6 and decreased neurotrophin-3 and interleukin-10 by EPINCSC
78	Lan et al, 2021 (88)	oxoproline-5 و BMSC	The optimal amount of 5-oxoproline for diagnosis of acute ischemic stroke is 3.127 μg/ml Protective role of BMSCs in ischemic stroke through GSH upregulation 5-oxoproline a potential biomarker for acute ischemic stroke
79	Paudyal et al, 2021 (89)	P5 و hADMSCs	No effect of hADMSCs and peptide on infarct volume Improvement in functional recovery in spatial learning and memory, bilateral coordination and sensorimotor function (rotating pole), and forelimb use asymmetry. Higher number of surviving graft cells in the peri-infarct area of animals treated with hADMSCs + P5 No increase in vascular density in peri-infarction area under influence of combined treatment
80	Zheng et al, 2021 (90)	extracellular vesicles derived from neural (NPC-EVs) progenitor cells	Reduction of cell damage by different doses of NPC-Evs Increase nerve recovery and nerve regeneration up to 3 months
81	Gong et al, 2022 (91)	(DPSCs) dental pulp stem cells	Improvement of neurological dysfunction, cerebral edema and reduction of infarct volume Decrease in percentage of TUNEL-positive nuclei Increase in number and percentage of NeuN positive cells
82	Hamblin et al, 2022 (92)	hNSC	Significant reduction of infarction Reducing the induction of pro-inflammatory factors and matrix metalloproteases Decreased expression of genes encoding TNF receptors, pro-inflammatory factors, apoptosis factors, adhesion and extravasation of leukocytes and Toll-like receptors
83	Sarmah et al, 2022 (93)	Intra-arterial Mesenchymal Stem Cell (MSCs IA)	Reduction in infarct size and improvement in functional and behavioral motor outcomes Average increase in neuron density and neuron length Increased expression of SIRT-1, BDNF and simultaneous decrease in the expression of various inflammatory and apoptotic markers

Based on obtained results, an increase in transcription factors and proteins such as VEGF, bFGF, SYP, BDNF, vascular endothelial growth factor, liver growth factor, nestin and connexin was observed after stem cell transplantation. Also, there was a decrease in expression and activity of pro-inflammatory factors such as tumor necrosis factor α, interleukin, adhesion molecules, as well as a decrease in the secretion of pro-inflammatory cytokinins such as TNFα, nitric oxide.

Both peripheral and innate immune responses contribute to neurodegeneration after stroke. Regulating peripheral inflammation can moderate brain inflammation after stroke. For example, splenectomy before MCAo reduces activated microglia and cerebral infarction. Systemic administration of minocycline reduces morphological activation of microglia in infarcted areas in stroke animals. Intravenous transplantation of human embryonic neural stem cells reduces systemic inflammatory responses and ameliorates neurological defects. Similar to peripheral inflammation, brain inflammation is also an important risk factor that leads to damage caused by stroke (52). Treatment with stem cells has a great potential to restore nerve function and reduce inflammatory response after ischemic brain injury (94). The therapeutic effect of transplanted neural stem cells may result primarily from neurotrophic effects that reduce inflammatory response and also suppress glial scar formation (54). Stem cells such as PDMC reduce IL-2-mediated IFN-g secretion as well as IL-2/NK-mediated apoptosis by upregulating HLA-G, an immunomodulatory molecule, after exposure to IFN-g. These data suggest that PDMCs may suppress inflammation through modulation of T cells and the IFN-g pathway in stroke brain (52).

Wang et al. reported that accumulation of F-FDG metabolite was a reason for improved performance in groups treated with transplanted cells. These researchers stated that transplanted stem cells integrate into tissue and replace damaged cells and rebuild nerve circuit. On the other hand, the number of neurons, astrocytes, and endothelial cells in iPSC treatment group was higher than in ESC treatment group, and angiogenesis caused by iPSC transplantation played an important role during recovery (36). Meanwhile, Koh and his colleagues suggested that the initial improvement observed in neurobehavioral function may be more related to neurotrophic factors secreted from injected MSCs than to a new network formation between the host neurons and transplanted MSCs. They also stated that these secreted neurotrophic factors may increase endogenous neurogenesis and reduce final infarct volume (15).

Bao and his colleagues also showed that transplantation of hBMSCs into brain parenchyma of mice with MCAO increased expression of BDNF, NT-3 and VEGF in ischemic brain, which was associated with reduction of infarct volume and improvement of neurological function. The possible mechanisms underlying these beneficial effects were increasing the proliferation of neural progenitor cells in SVZ and SGZ, accelerating migration of newborn neuroblasts to IBZ, reducing apoptosis, and increasing differentiation of these cells into adult neural cells (28). Oh et al., also stated that some cells from transplanted ep-iPSC-NPCs have the potential to differentiate into neural and glial lineages, and these cells increase endogenous brain repair such as SVZ neurogenesis and improve post-stroke inflammation and glial scar formation. In this way, they improve behavioral performance in model mice. One of the therapeutic mechanisms of ep-iPSC-NPC transplantation is neuron replacement, which may be a prerequisite for improved function in stroke. NPCs are an attractive cell source for use in stroke therapy compared to other cell sources, such as MSCs, which have shown no evidence of neural differentiation in vivo (84).

On the other hand, the direct incorporation of UC-MSC into host vessels may be another mechanism to increase angiogenesis after cerebral ischemia. UC-MSCs have angiogenic potential, because they can form capillary structures and differentiate into vascular cells. Angiogenesis requires the sprouting of new capillaries from pre-existing vessels in which endothelial cells retain their ability to proliferate. Incorporation of UC-MSC into vasculature and transformation into endothelial cells may increase the number of cells in the “endothelial cell pool,” thus enhancing sprouting angiogenesis. In addition, smooth muscle cells, pericytes and extracellular matrix are very important for vascular regeneration and maturation (18). Mitkari and colleagues reported that they observed an increase in the number of blood vessels in the prolesion area in MCAO rats when BMMSCs were injected 7 days after ischemia. Therefore, acute inflammatory processes may reduce the therapeutic effect when cells are administered immediately after ischemia. It is also plausible that injected BMMSCs counteract the decrease in angiogenic factors commonly seen after stroke over time and thus contribute to the increase in angiogenesis seen on postoperative day 43 (40). In a study by Wu et al., it was reported that there was an increase in vascular density in the ischemic areas of BMSC-transplanted animals, which, in conjunction with a reduction in cell apoptosis and scar size, may have contributed to the measured improvements in neurological function (20).

Based on the results of the study by Liu and his colleagues, modification with SVV increases the survival of transplanted mesenchymal stem cells, regulates the expression of VEGF and bFGF in cerebral ischemic tissues, reduces the infarct volume, and finally Improves neurological function in mouse stroke model. MSCs can improve neural function after stroke by promoting nerve regeneration. Several factors may be involved in the very low survival capacity of transplanted mesenchymal stem cells, such as severe inflammatory reaction and oxidative stress, a large amount of pro-apoptotic factors and chemokines (32). Yamaguchi et al. reported that the level of BDNF and PDGF-BB is negatively correlated with the age of transplanted cells and potentially reduces healing capacity, young MSCs show better healing behavior by preventing atrophy. Comparing the treatment with young hMSCs compared to old hMSCs, the results showed that the anti-inflammatory effects and vascular development by young hMSCs are increased and the migration of endogenous neural progenitor/stem cells has a positive relationship with astrocyte alignment. Accumulation of toxic metabolites, DNA damage, epigenetic changes, accumulation of damaged proteins and mitochondrial disorders have been observed in the stem cells of elderly donors. (72). Souza and colleagues reported that minocycline is a highly effective inhibitor of microglia activation in rodent experimental models of acute neurological disorders. Microglial inhibition is also related to decreased levels of TNF-α and other pro-inflammatory cytokines released by glial cells. Another important mechanism of the effect of minocycline is the inhibition of the box 1 protein, which acts as a cytokine and is vital for the inflammatory actions of microglial cells. Increasing the amount of BMMC in the tissue and better modulating the inflammatory response reduces the level of the lesion (62).

Conclusion

In studies reviewed, transplanted stem cells had various positive effects and were effective in improving the condition of model rats with ischemic stroke in different ways. These cells reduce infarct volume, decrease number of microglial cells, amount and symptoms of apoptosis, increase the amount of angiogenesis and vascular density in damaged area, migration of transplanted cells to damaged area, improve neurological, behavioral and sensorimotor function, increase transcription factors and Proteins such as VEGF, bFGF, SYP, BDNF, vascular endothelial growth factor, liver growth factor, nestin, connexin, reducing the expression and activity of proinflammatory factors such as tumor necrosis factor α, interleukin, adhesion molecules and also reducing the secretion of pro-inflammatory cytokines such as TNFα Nitric oxide works in improving the destructive effects of ischemic stroke. Therefore, stem cell therapy can improve the deficits of neural function and infarct volume and exert a potential neuroprotective effect for experimental ischemic stroke.

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