Reference Library
Exosomes in Stroke

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Clinical Trial of Mesenchymal Stem Cell exosomes for ischemic stroke

1. ***Mendt M, Rezvani K, Shpall E. Mesenchymal stem cell-derived exosomes for clinical use. Bone Marrow Transplant. 2019;54(Suppl 2):789–792. doi:10.1038/s41409-019-0616-z***

"The most recent clinical trial (NCT03384433) will begin accrual in October 2018. Led by Zali et al. at the Shahid Beheshti University of Medical Sciences, the study aims to determine the safety and efficacy of bone marrow MSC-derived exosomes genetically manipulated to con- tain miR-124 in patients with acute ischemic stroke. A recent preclinical study showed that MSC-derived exosomes loaded with miR-124 ameliorated brain injure, promoted neurovascular recovery after stroke, and pre- vented postischemic immunosuppression in mice [27]. The Phase 1/2 clinical trial aims to determine the bene- ficial effect of MSC-derived exosomes transfected with miR-124 administrated 1 month after the stroke, via ste- reotactic guidance into the ischemic area. Five patients will receive a single dosage of 200 mg total protein of allogenic MSC-derived exosomes loaded with miR-124. The primary endpoint is safety in the first 12months following therapy with documentation of adverse events including progressive or recurrent stroke, brain edema, seizures, and ischemic to hemorrhagic transformation. The secondary outcome, efficacy will be measured by the improvement in the modified Rankin Scale during the first year posttreatment."

2. Chen J, Chopp M. Exosome Therapy for Stroke. Stroke. 2018 May;49(5):1083-1090. doi: 10.1161/STROKEAHA.117.018292. Epub 2018 Apr 18. Review. PubMed PMID: 29669873; PubMed Central PMCID: PMC6028936.

"Compared to cell-therapy, the advantages of exosome-based therapy include[9, 14]: 1) low immunogenicity[56]; 2) no vascular obstructive effect, and reduced risk of secondary microvascular thrombosis[14]; 3) systemically injected exosomes are able to cross the BBB and enter the brain parenchyma[67, 68]; 4) the potential to develop large scale cellular factories of engineered therapeutic vesicles[17]; 5) exosomes have higher surface/volume ratio and amplify ligand gated signaling pathways and the transfer of biomolecules from stem cells to target tissues; 6) ability to readily modify exosome microRNA (miR) content."

3. Chang YH, Wu KC, Harn HJ, Lin SZ, Ding DC. Exosomes and Stem Cells in Degenerative Disease Diagnosis and Therapy. Cell Transplant. 2018 Mar;27(3):349-363. doi: 10.1177/0963689717723636. Epub 2018 Apr 25. Review. PubMed PMID: 29692195; PubMed Central PMCID: PMC6038041.

"Exosomes of miR133b-overexpressed MSCs have recently been reported to improve neural plasticity and functional recovery in a stroke model"[164,168]

"Intravenous injection of MSC-derived exosomes could improve functional recovery and neurite remodeling, neurogenesis, and angiogenesis[163]."

4. ***Zhang ZG, Chopp M. Exosomes in stroke pathogenesis and therapy. J Clin Invest. 2016 Apr 1;126(4):1190-7. doi: 10.1172/JCI81133. Epub 2016 Apr 1. Review. PubMed PMID: 27035810; PubMed Central PMCID: PMC4811130.***

"Intravenous administration of MSC-derived exosomes to rats subjected to focal cerebral ischemia or TBI substantially improved neurological function by promoting neurovascular remodeling during stroke and TBI recovery (116, 117, 119). Therapeutic effect of MSC-derived exosomes has also been demonstrated by independent laboratories in the mouse subjected to stroke and TBI (114, 115). Systemic administration of MSC-derived extracellular vesicles to ischemic mice markedly reduced motor coordination deficits and enhanced angiogenesis and neurogenesis, while treatment of TBI mice with human MSC- derived extracellular vesicles substantially preserved spatial leaning ability (114, 115). Intravenous administration of tailored MSC-derived exosomes with increased or decreased miR-133b to rats with stroke led to enhancement or exacerbation, respectively, of axonal remodeling and neurological function compared with naturally occurring MSC-derived exosomes (119)."

5. ***Sarko DK, McKinney CE. Exosomes: Origins and Therapeutic Potential for Neurodegenerative Disease. Front Neurosci. 2017;11:82. Published 2017 Feb 27. doi:10.3389/fnins.2017.00082***

Mesenchymal stem cell-derived exosomes are shown to yield tissue-protective effects in stroke models following neural injury resulting from middle cerebral artery occlusion (Xin et al., 2012). Neurite branch number and length was shown to increase significantly following delivery of mesenchymal stem cell-derived exosomes (Yu et al., 2011). This success presumably resulted from exosomal transfer of microRNA 133 b that has been shown to facilitate neuronal recovery following spinal cord injury (Yu et al., 2011).

6. ***Osier N, Motamedi V, Edwards K, et al. Exosomes in Acquired Neurological Disorders: New Insights into Pathophysiology and Treatment. Mol Neurobiol. 2018;55(12):9280–9293. doi:10.1007/s12035-018-1054-4***

"miR-126 levels are informative for detecting cerebral ische- mia, serum levels increased sensitivity to qualifying the sever- ity of ischemia [23] The finding that MSCs and MSC-EVs comparably promoted neurogenesis and angiogen- esis post-stroke might suggest that the active component of MSC therapy is due in part to the administration of exosomes, though this remains to be empirically established [20]. . In this study of pre-term brains, the therapeutic administration of MSC-EVs reduced the number and duration of seizures; MSC-EVs also preserved the sensi- tivity of the baroreceptor reflex, which was associated with an observed tendency to prevent hypo-methylation. . A key finding of this study is that BYHWD-treated exosomes resulted in higher expression of angiogenic miRNA in cell culture; in the rat model, expression of vascular endo- thelial growth factor (VEGF) and Ki-67 (also known as MKI67) was increased, which was associated with augmented vascular density after stroke [17]. "

"The fifth and final study examined exosomes using 65 acute ischemic stroke patients and 66 healthy volunteers who did not have a history of stroke [18]. Patients provided serum samples which were used to isolate exosomes, and western blot analysis was used to assess levels of established exosomal markers (CD9, CD63, and CD81) [18]. When compared to controls, individuals with stroke had signifi- cantly higher concentrations of exosomes in serum, as well as significantly (all p's < 0.01) higher median levels of miR- 9 and miR-124, two micro-RNAs implicated in regulation of gene expression [18]. A second key finding was that exosomal levels of both miR-9 and miR-124 were positively correlated with total score on the National Institutes of Health Stroke Scale and were also correlated with the overall volume of the infarct as well as the concentration of the in- flammatory biomarker interleukin (IL)-6 in serum [18]. Overall, this study suggested that exosomes obtained from serum samples are helpful in identifying patients with acute ischemic stroke and can be used to gain insights into the likely extent of damage [18]. "

7. Hong ***SB, Yang H, Manaenko A, Lu J, Mei Q, Hu Q. Potential of Exosomes for the Treatment of Stroke. Cell Transplant. 2019;28(6):662–670. doi:10.1177/0963689718816990***

Table 2. Exosomes as Therapy Agents in the Treatment of Ischemic Stroke.

Source	Disease model	Contents	potential target	Assessment standards	Ref.(PMID)
BM-MSCs	Photothrombosis model in mice	miR-124	Gli3 and STAT3 in ischemic tissue	Immunohistochemistry of Sox2, Nestin and DCX	28624203
miR-133b^{+} MSCs	MCAO in rats and OGD model in Primary Astrocyte	miR-133b	Astrocytes	A foot-fault test and a modified mNSS test. Immunohistochemical staining in the IBZ	27677799
miR-133b^{+} MSCs	MCAO in rats	miR-133b	Connective tissue growth factor and ras homolog gene family member A in the IBZ	The adhesive-removal test and foot-fault test for rats	23630198
miR-17-92^{+} MSCs	MCAO in rats	miR-17-92	PTEN Akt, mTOR and GSK-3β	A mNSS and foot-fault tests, histochemistry, immunohistochemistry and Golgi-Cox staining in the IBZ	28232590
CDCs	Rabbit small-clot embolic stroke model	miR-146a, miR-181b, and miR-126	Superoxide dismutase-2,	Clinical rating scores and quantal analysis	29908146
miR-30d-5p^{+} ADSCs	OGD and murine models of MCAO	miR-30d-5p	Microglial	Immunofluorescence and luciferase reporter assay	29807362

BM-MSCs: bone marrow mesenchymal stem cells; MSCs: mesenchymal stem cells; CDCs: cardiosphere-derived cells; ADSCs: adipose-derived stem cells; MCAO: middle cerebral artery occlusion; OGD: oxygen and glucose deprived; Gli3: glioma-associated oncogene family zinc finger 3; STAT3: signal transducer and activator of transcription 3; IBZ: infarction border zone; PTEN: phosphatase and tensin homolog; AKT: protein kinase B; mTOR: mammalian target of rapamycin; GSK-3β: glycogen synthase kinase 3 beta; DCX: doublecortin; mNSS: modified neurologic severity score.

8. Liu W, Bai X, Zhang A, Huang J, Xu S, Zhang J. Role of Exosomes in Central Nervous System Diseases. Front Mol Neurosci. 2019;12:240. Published 2019 Oct 4. doi:10.3389/fnmol.2019.00240

TABLE 1 | Biomarkers in exosomes associated with stroke.

Source	Contents	Mechanism	Clinical application	References
Peripheral blood	cystatin *C*, CD14, alpha-lib and talin-1	Vascular event	Early diagnosis	Datta et al., 2014; Kanhai et al., 2014
Serum	caspase-1	Inflammation	Severity judgment	Kerr et al., 2018
Serum	miR-126	Angiogenesis	Severity judgment	Chen et al., 2015; Osier et al., 2018
Plasma	miR-124	Neurogenesis	Early diagnosis	Mishima et al., 2007; Mirzaei et al., 2018
Plasma	miR-30a-5p and miR-21-5p	Inflammation	Early diagnosis, severity judgment and prognosis	Hong et al., 2018; Jiang et al., 2018

caspase-1, inflammatory protein.

TABLE 2 | Biomarkers in exosomes associated with neurodegenerative disease.

Name of disease	Source	Contents	Mechanism	Clinical application	References
Alzheimer's disease	Plasma and CSF	Aβ and NFT	Neuronal damage	Early diagnosis	Wang et al., 2017; Xiao et al., 2017
Alzheimer's disease	Plasma	REST, HSF-1, Lamp 1 and IRS	Neuronal damage	Early diagnosis	DeLeo and Ikezu, 2018; Pluta and Ulamek-Koziol, 2019
Alzheimer's disease	Serum	miR-135a, miR-193b and miR-384	Neuronal damage	Early diagnosis	Goetzl et al., 2015b
Parkinson's disease	CSF	α - SYN, DJ-1 miR-1, miR-485-5p, miR-153, miR-409-	Neuronal damage	Early diagnosis	Joshi et al., 2015; Li et al., 2019
Parkinson's disease	CSF	3p, miR-433, miR-136-3p, let-7g-3p, miR-19b-3p, miR-10a-5p, miR-132-5p, miR-370 and miR-873-3p	Neuronal damage	Early diagnosis	Yang J. et al., 2017
Prion Diseases	Plasma	PrPSc	Neuronal damage	Early diagnosis	Hartmann et al., 2017
Prion Diseases	Serum	miR-142-3p, miR-143-3p, miR-145a-5p, miR-451a, miR-146a-5p, miR-150-5p, miR-320, miR-let-7b, miR-141-3p, miR-429-3p and miR- 200 family	Neuronal damage and inflammation	Early diagnosis and severity judgment	Reza-Zaldivar et al., 2018; Shah et al., 2018
Amyotrophic lateral sclerosis	Peripheral blood and CSF	TDP-43	Neuronal damage and inflammation	Early diagnosis	Iguchi et al., 2016
Amyotrophic lateral sclerosis	Plasma	miR-183-5p, miR-9-5p, miR-193a-5p and miR- 15a-5p	Neuronal damage	Early diagnosis	Saucier et al., 2019
Huntington's disease	Plasma	mHtt	Neuronal damage	Early diagnosis and severity judgment	Wang et al., 2017; Denis et al., 2018
Huntington's disease	Plasma	miR-877-5p, miR-223-3p, miR-30d-5p, miR-128, miR-22-5p, miR-223-5p, miR-222-3p, miR-338-3p, miR-130b-3p, miR-628-3p, miR-361-5p, miR-425-5p	Neuronal damage	Early diagnosis	Kumar et al., 2017

CSF, cerebrospinal fluid; Aβ plaque, aggregation of beta-amyloid protein; NFT, neurofibrillary tangles; α-SYN, alpha-synuclein; DJ-1, oxidative stress sensor; PrPSc, misfolded prion protein; TDP-43, a protein that helps regulate gene expression; mHtt, produces mutant Huntington protein.