

Stem cell therapy in ischemic stroke

Role of IV and intra-arterial therapy

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ABSTRACT

Objective: Cell-based therapies are being investigated as an adjunct to IV thrombolysis or mechanical thrombectomy in ischemic stroke. This review summarizes the potential applications as well as challenges of intravascular cell delivery in ischemic stroke.

Method: We conducted a search of Medline as well as the clinicaltrials.gov Web site for all ongoing human clinical studies using stem cells in ischemic stroke patients.

Result: The pros and cons of the various donor cell types and routes of cell delivery, including intravascular delivery, in ischemic stroke are discussed. In addition, the potential challenges in translation from bench to bedside, the optimal techniques for intravascular cell delivery, and an updated comprehensive list of ongoing clinical trials in ischemic stroke are highlighted.

Conclusions: Stem cells have shown a promising role in ischemic stroke, in preclinical studies as well as initial pilot studies. Further studies are needed to assess intravascular cell therapy as a potential adjunct to thrombolysis or mechanical thrombectomy in ischemic stroke. *Neurology*® 2012;79 (Suppl 1):S207-S212

GLOSSARY

BMMNC = bone marrow mononuclear cell; **IA** = intra-arterial; **IC** = intracerebral; **ICV** = intracisternal/cerebroventricular.

Cell therapy is emerging as a promising new modality for enhancing neurologic recovery in ischemic stroke.¹ Numerous basic science studies have demonstrated positive results in animal models of ischemic stroke following implantation of progenitor cells derived from various sources, including adipose, human fetal/embryonic tissue, bone marrow, peripheral, and umbilical cord blood (figure).² These animal studies have utilized various methods of cell delivery or implantation (table 1), including direct intracerebral (IC) injection, intracisternal/cerebroventricular (ICV), or intravascular routes of delivery such as IV or intra-arterial (IA) infusion.

Methods of cellular delivery and implantation. Intracerebral. Direct injection is invasive, and despite being a precise method of cellular delivery and implantation, it results in a poor distribution of cells in the target lesion.³ Initial pilot human studies investigating stereotactic IC cell implantation in patients with chronic stroke also reported adverse events, including seizures, syncope, asymptomatic subdural hematoma, transient motor worsening, and enhancing lesions on MRI.^{4,5}

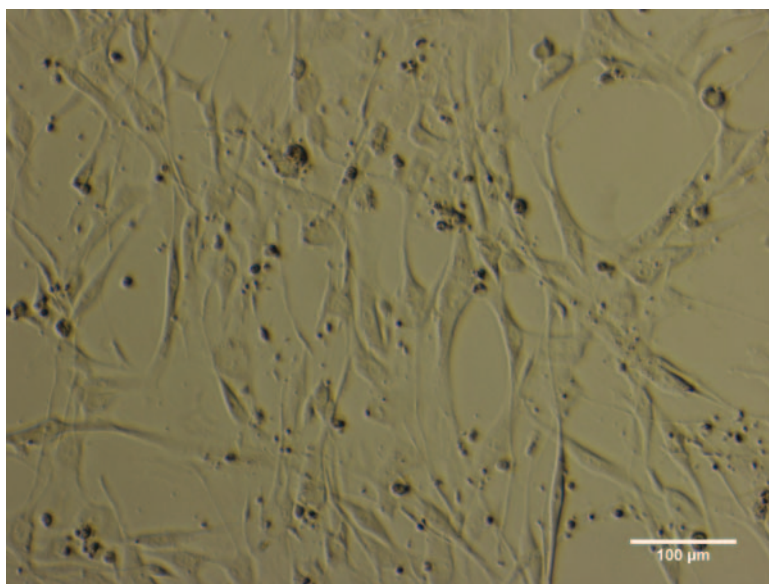
Intracisternal/cerebroventricular. The ICV route of cell delivery is less invasive than direct IC implantation but is also associated with variable cell migration to the ischemic site.^{6,7} In a pilot human study investigating ICV delivery in 10 chronic stroke patients (7 ischemic and 3 hemorrhagic), some patients developed fever and meningeal signs 48 hours after cellular delivery via ICV route.⁸

IV. Infusion is the least invasive method, allowing wide distribution of cells with exposure to chemotactic signals that potentially guide them toward the target ischemic lesion. This method, however, results in cells being trapped by peripheral organs, including the lungs, liver, and spleen, thereby limiting potential engraftment in the ischemic lesion in the brain.² Since patients with ischemic stroke commonly have associated cardiac and renal impairment, there is also a potential for the cells reaching these organs, with further reduction in cell delivery to the ischemic brain.^{9,10} Given that IV cell delivery is least invasive, this method of

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Figure Phase contrast image of human umbilical cord blood stem cells



delivery has been investigated in patients with chronic stroke. In a placebo-controlled phase I/II trial of 30 patients with chronic stroke, 5 in the treated group received autologous mesenchymal stromal cells at 1 to 2 months from the onset of symptoms. This method was reportedly safe and feasible

in the short term,¹¹ as well as on long-term follow-up, with improved neurologic recovery in those patients receiving cellular therapy.¹² Another unblinded single-arm study demonstrated safety and feasibility with IV infusion of autologous mesenchymal cells in 12 patients post-stroke onset (range, 36–133 days).¹³ Until recently, all human studies had reported results in chronic stroke patients. Recently, an open-label prospective human study demonstrated safety and feasibility with IV mononuclear cell infusion in 10 patients with acute stroke.¹⁴ Patients in this study underwent bone marrow harvest and subsequent IV cell infusion within 24 to 72 hours of stroke onset. This methodology is supported by a preclinical study in which rats with common carotid artery/middle cerebral artery occlusion performed better on neurologic tests with IV mononuclear cells infused up to 72 hours, compared with 1 week from stroke onset.¹⁵ However, similar to prior animal experiments, this study also found cells sequestered in the spleen, lung, liver, and kidney.

Intra-arterial. Cell delivery involves endovascular infusion of progenitor cells directly in the artery perfusing the ischemic tissue. This route of cell delivery also bypasses the peripheral filtering organs, thereby increasing cell delivery to the target ischemic tissue with uniform distribution. Animal studies have demonstrated higher rates of cell engraftment with IA delivery,^{16,17} as well as a higher concentration of cells in the target ischemic lesion with IA,¹⁶ compared with IV cell infusion.^{18,19} One preclinical study comparing IV and IA autologous bone marrow mononuclear cell (BMMNC) delivery found significant reduction in infarct volume, higher cell engraftment, and improved motor function with IA delivery.²⁰ The authors attributed this “significant neuroprotective effect” in the IA group to the larger number of implanted cells in the brain during early reperfusion. Despite the advantage of increased cell homing in the ischemic lesion, few animal studies have also raised concern with the potential for microvascular occlusion, worsening ischemia, and higher mortality with IA delivery.^{19,21} A recent preclinical study investigated the etiology of cerebral blood flow reduction and microvascular occlusion following IA neural progenitor cell infusion.²² The investigators attributed the microstrokes to the prior procedural technique, but that can be overcome with preserved anterograde flow.²²

Mechanisms of action of stem cells in ischemic stroke. Preclinical studies on the use of stem cells for the treatment of stroke have now clearly demonstrated that the administration of different types and sources of stem cells can ameliorate neurologic deficits, and in some cases significantly reduce the size of the infarct. For example, IV administration of human cord

Table 1 Routes of cell delivery

Route	Pros	Cons	Cell types used in pilot human studies
IC	Precise method of implantation	Invasive	Human neuronal, fetal porcine
		Nonuniform distribution in the ischemic lesion	
		Reported adverse events in pilot human studies	
ICV	Less invasive than IC	Potential for bleeding risks in stroke patients receiving antiplatelets or anticoagulants	Immature neuronal and hemopoietic
		Variable cell migration in ischemic lesion	
		Reported adverse events in a human study, including meningitis	
IV	Most feasible route; least invasive and found safe in pilot human studies	Potential for bleeding risks in stroke patients receiving antiplatelets or anticoagulants	Autologous mesenchymal stromal; autologous bone marrow mononuclear
		Poor cell engraftment at the cerebral ischemic lesion due to sequestration in peripheral filtering organs (such as lung capillaries)	
IA	Less invasive than IC and ICV; high rates of cell engraftment with uniform distribution at the ischemic site	Potential for microvascular occlusions	Autologous bone marrow mononuclear

Abbreviations: IA = intra-arterial; IC = intracerebral; ICV = intracisternal/cerebroventricular.

Table 2 Donor cell types

Cell sources and types	Pros	Cons
1. Bone marrow, autologous	Lack of immune rejection	Need bone marrow harvest
		Need specialized labs for cell separation and processing
		Not readily available for infusion in acute situations
2. Bone marrow, allogeneic	Readily available for infusions in acute situations	Potential risk of rejection
		Need bone marrow harvest
		Need specialized labs for cell separation and harvesting
3. Umbilical cord, mononuclear	Could be readily available in the acute stroke setting	Requires large numbers of donors
		Low passage number
		Need specialized labs for cell separation and processing
		Potential risk of rejection
4. Umbilical cord, stem	Could be readily available in the acute stroke setting	Need specialized labs for cell separation and processing
		Potential risk of rejection
5. Embryonic stem	Potential for neural replacement	Ethical concerns
	Could be readily available in the acute stroke setting	Potential teratoma formation
		Need specialized labs for cell separation and processing
6. Induced pluripotent stem, autologous	Lack of immune rejection	Potential teratoma formation
		Need specialized labs for cell separation and processing
		Not readily available in the acute setting
7. Induced pluripotent stem, allogeneic	Could be readily available in the acute stroke setting	Risk of rejection
		Potential teratoma formation
		Need specialized labs for cell separation and processing
8. Direct reprogramming of somatic cells, autologous	Lack of immune rejection	Need specialized labs for cell separation and processing
		Not readily available in the acute setting
9. Direct reprogramming of somatic cells, allogeneic	Could be readily available in the acute stroke setting	Risk of rejection
		Need specialized labs for cell separation and processing

blood stem cells into laboratory rodents 2 days after ischemic stroke has been shown to reduce infarct lesion volume by approximately 50% and improve neurologic function by approximately 55%.²³

Early studies of stem cell therapy for treating stroke were based on the rationale of replacing neural cells that were lost as a result of ischemic brain injury. These cells could be neuronal, astrocytic, oligoden-

droglial, or endothelial in phenotype. However, it has now become clear that in spite of improvements in neurologic outcome and reductions in infarct size, the mechanism of cell replacement in stem cell therapy for stroke appears to play a more modest role than originally envisioned. Recent reports have shown that the administration of stem cells in animals with stroke can induce the reinstatement of functional connectivity, as determined by functional MRI.²⁴ This, in turn, may be mediated by the outgrowth of nerve fibers of endogenous neurons.^{23,25} Other studies have demonstrated that stem cell therapy results in the upregulation of growth factors that may be responsible for the outgrowth of these endogenous fiber processes²⁶ and for the inhibition of inflammatory processes,²⁷ which may lead to secondary cell loss within the brain. These observations offer intriguing alternative mechanisms that may underlie the restorative effects noted with stem cell therapy following stroke and provide a rationale basis for clinical trials.

Challenges in translating intravascular cellular delivery from bench to the bedside. All routes of cell delivery have appeared promising in animal studies, although the intravascular routes of delivery such as IV and IA are less invasive than IC and ICV routes. Despite promising results in animal studies, several key questions remain to be answered before proceeding to human trials, such as choice of cells for delivery or implantation (table 2), the timing of cellular therapy, and the dose of cells delivered or implanted. Despite these knowledge gaps, initial clinical trials investigating cell therapy in chronic as well as sub-acute strokes have already begun worldwide (table 3).

Choice of cells. The authors describe the pros and cons of the various donor cell types and their relevance to acute ischemic stroke (table 2). The longer timeframe required for obtaining cells from autologous sources limits their potential application in patients with hyper-acute strokes. Cells derived from umbilical cord^{23,28} or placenta²⁹ could be potentially investigated in clinical studies in patients receiving IV or IA thrombolytic therapy in the initial few hours after a stroke.

Timing of cell therapy. Unlike IV or IA revascularization therapies, there are no clearly defined therapeutic time windows for cell therapy with all routes of delivery. Since most ongoing human studies use cells from autologous sources, these trials are investigating therapeutic windows ranging from a few days to several months.

Dose. Preclinical studies have demonstrated a dose–response relationship, with higher IV cell dose resulting in smaller infarct volumes.^{30–31} Given that IV infusion results in sequestration of cells in peripheral organs, it is theoretically conceivable that IA de-

Table 3 Ongoing clinical trials

Study phase	Mode of delivery	Cell type	Time from onset	Primary outcome measure	Secondary outcome measure	Institution	Location	Clinicaltrials.gov identifier
I	IC	CTX0E03 neural stem	6 mo–5 y	Safety	Functional outcome	Glasgow South General Hospital	United Kingdom	NCT01151124
I/II	IC	Modified stem, SB623	6–12 mo	Safety	Functional outcome	Stanford University, University of Pittsburgh	United States	NCT01287936
II	IC	Autologous peripheral CD 34 + stem	>6 mo, <60 mo	Functional outcome	Functional outcome, imaging	China Medical University Hospital	Taiwan	NCT00950521
I	IV, IT	Umbilical cord, mesenchymal	IV, 7–14 d; IT, 1 wk after IV	Functional outcome	Evoked potentials and MRI changes	General Hospital of Chinese Armed Police Forces	China	NCT01389453
I/IIa	IV	Autologous bone marrow mononuclear	24–72 h	Safety, feasibility	Functional outcome	University of Texas at Houston (UT)	United States	NCT00859014
I/IIa	IV	Autologous mesenchymal stem	Within 6 wk	Safety, feasibility	Functional outcome	United States Hospital, Grenoble	France	NCT00875654
I/II	IV	Ex vivo cultured adult allogenic mesenchymal stem cells	Within 10 d	Safety	Functional outcome, Infarct volume	Multicenter-Stempeutics Research, Malaysia	Malaysia	NCT01091701
I/II	IV	Mesenchymal bone marrow cells	>6 mo	Safety	Functional outcome	United States: California, San Diego	United States	NCT01297413
IIa	IV	Human placenta-derived, PDA001	Acute to subacute	Safety	Functional outcome	Chattanooga Center for Neurological Research	United States	NCT01310114
I	IV, IA	Autologous bone marrow mononuclear	>3 h and <90 d	Safety, feasibility	Functional outcome	Federal University of Rio de Janeiro	Brazil	NCT00473057
I/II	IA	Autologous bone marrow CD 34 + stem	Days 5– 9	Safety	Functional outcome	Hospital Universitario Central de Asturias	Spain	NCT00761982
II	IA	ALD-401 from autologous bone marrow	13–19 d	Safety	Functional outcome	University of Texas at Houston, Duke University, LA Brain & Spine Institute	United States	NCT01273337
I/II	IA	Autologous bone marrow CD 34 + stem	7 d	Safety	Functional outcome	Imperial College, London	United Kingdom	NCT00535197

Abbreviations: IA = intra-arterial; IC = intracerebral; IT = intrathecal.

livery could produce similar results with lesser cell doses; however, the optimal dose for IV or IA therapy is unclear. The initial clinical studies have essentially focused on feasibility of autologous cell procurement and the maximum viable cell dose that could be safely obtained prior to delivery.

Intra-arterial cell delivery in cardiac and peripheral vascular disease. Numerous initial clinical studies investigating IA cell delivery in patients post–myocardial infarction have demonstrated a trend toward improved clinical outcomes as well as physiologic parameters (increased contractility and improved myocardial perfusion, with decreased infarct size and end-systolic volume).³² These studies primarily utilized autologous bone marrow–derived cells and did not report any significant adverse events. Along similar lines, patients with peripheral vascular disease treated in clinical studies with IA or combined IA and IM injections of autologous bone marrow cells have demonstrated favorable outcomes so far.³³ These studies also reported no significant adverse events, with improved ankle-brachial index, decreased claudication, and improved walking distance.

Preliminary human experience with intra-arterial cell delivery in ischemic stroke. In the first reported case of IA cell delivery in ischemic stroke, the authors performed IA autologous BMMNC infusion in a patient with left middle cerebral artery distribution infarct, 3 days after symptom onset.³⁴ Prior to infusion, transcranial Doppler demonstrated intracranial arterial patency. The authors also reported a decrease in hypoperfusion on SPECT as well as increased metabolism in the ischemic tissue, 7 days after IA cell delivery. They subsequently reported another patient who underwent IA autologous BMMNC delivery in the left middle cerebral artery 9 days after stroke onset.³⁵ They also labeled 1% of these cells with Tc-99m by incubating with hexamethylpropylene amine oxime and subsequently performed SPECT scanning, 8 hours following the IA infusion. They reported good clinical recovery and also mentioned that this method of in vivo cell tracking could be safe in humans after IA delivery.

More recently, a pilot study reported safety in IA BMMNC delivery in the middle cerebral artery in patients with chronic stroke.³⁶ They reported no

symptomatic worsening or significant adverse effects. One patient developed asymptomatic spike-wave activity following infusion. Two patients developed seizures 6 months after infusion, which were deemed unrelated to the infusion and treated with antiepileptic drugs.

Optimal endovascular techniques for intra-arterial cell delivery in ischemic stroke. As demonstrated by pre-clinical studies, prespecified endovascular technical details are the key to safety of this route of cell delivery. In patients with myocardial infarction receiving intracoronary cell delivery, the interventionalists used an over-the-wire single balloon catheter that was inflated to occlude flow for a few minutes, during which the cells were infused in the coronaries distal to the occlusion through the lumen of the balloon catheter. This maneuver was performed to allow for adhesion and transendothelial migration of the infused cells.³⁷ The balloon would then be deflated to allow antegrade coronary flow, and this procedure was repeated until all the cells were delivered. Similarly, a double-balloon occlusion technique with ports in between the 2 balloons has been used for IA delivery of a high concentration of chemotherapeutic agents.³⁸ Although the single or double balloon techniques have shown promise,^{37,38} this might not necessarily be the case in the more fragile cerebral blood vessel.³⁹ As demonstrated recently in a preclinical study, preserved antegrade flow in the parent artery during IA cell delivery might be a safer technique in the craniocerebral vasculature.²²

It is critical to have pre-established flow rates that do not affect viability of specific stem cells, with use of different microcatheters, heparinized saline, and angiographic contrast agents. A study has demonstrated that infusion of 10 million cells/mL through the Excelsior SL-10 microcatheter (Boston Scientific, Fremont, CA) at rates of up to 2 mL/min under standard temperature conditions did not affect viability of BMMNCs.⁴⁰ Cell viability was also unaffected with exposure to Omnipaque (Nycomed, Princeton, NJ) and low-dose heparin (2.5 U/mL) for 1 hour. There was a noticeable reduction in viability of BMMNCs at a concentration of 10 million cells/mL with infusion rates in excess of 2 mL/min and exposure to high-dose heparin (500 U/mL) for 1 hour. Another study demonstrated that infusion of human umbilical cord blood cells through the Excelsior SL-10 microcatheter (Boston Scientific) at concentration of 10 million cells/mL led to a reduction in viability.⁴¹ There was no effect on viability of these cells at a concentration of 1 million cells/mL, regardless of flow rates.

DISCUSSION Cell-based therapy is a potential adjunct therapeutic modality to acute revascularization

therapies (IV thrombolysis or mechanical thrombectomy) for improved neurologic recovery in stroke patients. Despite the challenges in clinical translation from basic science studies, initial pilot studies have demonstrated safety and feasibility with IV and IA cell delivery. The ongoing clinical trials using various delivery routes, choice of cells, timing of therapy, and doses of cells are likely to bridge the knowledge gaps that exist with this therapy for patients with ischemic stroke.

AUTHOR CONTRIBUTIONS

Dr. Misra: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Mr. Ritchie: drafting/revising the manuscript, analysis or interpretation, acquisition of data. Ms. Stone and Dr. Low: drafting/revising the manuscript, study concept or design. Dr. Janardhan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

DISCLOSURE

Dr. Misra reports no disclosures. Mr. Ritchie holds stock in Novartis AG. Ms. Stone reports no disclosures. Dr. Low holds patents for biomarkers for ovarian cancer and biomarkers for breast cancer; serves as a consultant for Saneron CCEL; receives research support from NIH and HRK Foundation; receives research support from the University of Minnesota, AOSpine, International Organization of Glutaric Aciduria, and Gateway Foundation; and holds stock or stock options or expense compensation for serving on a board of directors from Saneron CCEL. Dr. Janardhan reports no disclosures. **Go to Neurology.org for full disclosures.**

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