

Restorative Therapies after Stroke: Drugs, Devices, and Robotics

M. V. Padma Srivastava¹ Neha Kuthiala¹

¹Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence M. V. Padma Srivastava, MD, DM, FRCP, FAMS, FNAsc, FIAN, Department of Neurology, Neurosciences Center, Room Number 708, All India Institute of Medical Sciences, New Delhi 110029, India (e-mail: vasanthapadma123@gmail.com)

Ann Natl Acad Med Sci (India) 2019;55:124–131

Abstract

Restorative therapies aim to improve outcome by salvaging threatened brain, as with reperfusion or neuroprotective drugs and also by promoting plasticity within surviving neural tissue. Restorative therapies typically have a therapeutic time window measured in days and weeks and so have the potential to be assessed by a large fraction of patients with a new stroke. Examples of such brain repair therapies include growth factors, cell-based therapies, and devices. Positive clinical trials have been reported in human studies for several classes of restorative therapy after stroke. These include robotics, constrain-induced movement therapy (CIMT), and pharmacological therapy, such as levodopa and selective serotonin reuptake inhibitors. In addition, several forms of noninvasive cortical stimulation, such as rapid transcranial magnetic stimulation, transcranial direct current stimulation, and theta-burst stimulation, have shown promise in early phase studies. The current review gives a glimpse of the existing strategies, those on the anvil of implementation and those with a hope of launch in near future.

Keywords

- ▶ stroke
- ▶ stem cell therapy
- ▶ vascular endothelial growth factor
- ▶ physiotherapy

Introduction

Increased understanding of pathogenesis and pathophysiology of stroke in the last few decades has paved way for path breaking advances in bettering stroke outcomes.¹

The injury, repair, and recovery after stroke have been extensively defined.²⁻⁵ The first epoch is related to acute injury and takes place in the first initial hours after stroke when changes in blood flow, edema, metabolism rate, and diaschisis occurs. A second epoch is related to repair which starts days after stroke and lasts for several weeks and is referred to as endogenous repair suggesting a golden period for initiating restorative therapies. A third epoch occurs weeks to months after stroke when spontaneous recovery gains have plateaued and this represents a stable but modifiable late phase.^{6,7}

Unimodel targeting of key events in stroke pathophysiology has not been effective in providing long-term benefits, leading to negative results in previous clinical neuroprotective stroke trials.⁸ A successful future stroke therapy needs to approach multiple pathophysiological mechanisms besides

revascularization/reperfusion including thrombolytics related adverse side-effects, prevention of apoptosis (programmed cell death), stimulation of neuroregeneration, and neuronal plasticity.^{8,9}

Review

Acute Reperfusion Therapies after Ischemic Stroke

Thrombolytic therapy is an inherently attractive treatment for acute ischemic stroke (AIS), based on the known pathologic and angiographic substrates of ischemic cerebrovascular disease.^{10,11}

Emerging strategies include those that have the potential to extend cerebral reperfusion therapy beyond 4.5 hours of time window, as well as the means to bridge the “stroke recovery gap” (defined as the difference observed between the clinical response to thrombolytic therapy in a given population of patients presenting with ischemic stroke and the potential clinical recovery if all of the penumbra were salvaged under ideal circumstances).¹² Approaches to this include the following: (1) intra-arterial pharmacological reperfusion

approaches, combined intravenous–intra-arterial fibrinolysis, and combined fibrinolytics and glycoprotein IIb/IIIa agents¹²⁻¹⁴; (2) emerging endovascular mechanical reperfusion strategies including intra-arterial thrombectomy (clot retrieval devices and suction thrombectomy devices), mechanical disruption (microguide wire passage, laser photo acoustic emulsification, and primary intracranial angioplasty); (3) augmented fibrinolysis by endovascular ultrasound; (4) multimodal imaging with magnetic resonance (MRI) or computed tomography (CT) to rapidly assess the infarct core, penumbra, site of vessel occlusion, and tissue hemorrhagic propensity, enabling improved selection of patients for reperfusion therapy beyond any arbitrary fixed time window; (5) newer thrombolytic agents; (6) adjunctive therapies such as neuroprotectants.¹²

Endovascular treatment of acute ischemic stroke (AIS) is a therapy with a visible effect. With reperfusion, we know that in the right patient, our hemiplegic patients can walk out of hospital back into their lives. All the recent trials, for example, MR CLEAN, EXTEND-1A, SWIFT-PRIME, and REVASCAT, have all given unequivocal results in favor of endovascular intervention in selected patients. We have entered a new era of stroke therapy for major acute ischemic stroke.¹⁵⁻¹⁷ Endovascular treatment has become a new standard of care for large vessel AIS. We will need to adapt triage rules and process and train new and existing personnel. We will need to assess the medical aspects of care including the thrombolytic agents in combination with endovascular thrombectomy, anesthesia use, adjuvant antithrombotic therapy, and medical management of blood pressure.^{17,18} We need to properly identify the best imaging selection techniques because the association with outcome will not be confounded by the lack of reperfusion.

The single unifying theme will be speed. Onset to reperfusion time is the new bottom line process metric and we cannot compromise on this. This will remain the fundamental principle for AIS now and into the future.¹⁸

Stroke infrastructure must now adapt to endovascular therapy. As with intravenous (IV) recombinant tissue plasminogen activator (rTPA), only a small percentage of patients with stroke will require endovascular therapy (estimates are 10%), but this small percentage will drive the reorganization of systems of stroke care.¹⁸

The ultimate aim of any therapeutic strategy is maximum restoration possible and eventual return to normalcy of function. The nonregenerating aspect of an injured adult brain has been challenged in the recent past and neural plasticity documented in both global and focal models of animal ischemia.⁶

Cell Based Therapies

Biological basis for neurorestorative therapy poststroke are as follows:

- Neurorestoration poststroke is achieved by enhancing neurogenesis, angiogenesis, and oligodendrogenesis which in concert promote neurological recovery.¹⁹

- Neurogenesis, the generation of new parenchymal cells from neural stem cells (NSC), and progenitor cells stimulates plasticity.
- Oligodendrogenesis restores neuronal signal transduction and promote myelination.
- Angiogenesis and arteriogenesis increases cerebral blood flow perfusion and mediates the generation of important restorative trophic factors and proteases.¹⁹

Cell-based therapies under investigation include use of bone-marrow mesenchymal cells, cord blood cells, fetal cells, and embryonic cells. The common restorative characteristic of these therapies is that they target many types of parenchymal cells (including neural stem cells, cerebral endothelial cells, astrocytes, oligodendrocytes, and neurons), leading to enhancement of endogenous neurogenesis, angiogenesis, axonal sprouting, and synaptogenesis in ischemic brain tissue. These events collectively improve neurological function after stroke.²⁰

Stroke poses special conditions that impact the potential success of transplantation to enhance neurological recovery. An infarct might involve the thalamus, hippocampus, and striate cortex affecting three or more very different neuronal populations. Besides, neurons, oligodendrocytes, astrocytes, and endothelial cells are also affected. Reconstitution of the complex and widespread neuronal-glia-endothelial networks is a herculean task to say the least.

There is uncertainty about the mechanisms by which cell transplantation might improve stroke deficits. Transplanted cells would ideally replace cells that are damaged by ischemia and take over function of these cellular elements. However, it is also possible that transplanted cells secrete trophic factors that help to maintain marginally surviving cells or otherwise enhance the local environment to improve function.²¹⁻²⁵

How do Transplanted Cells Work?

In most cases of neural transplantation, it is likely that therapeutic effects of the implanted neurons or their precursors would be dependent upon their functional and structural integration into the brain tissue. However, the question is whether establishment of neural circuitry is the only means of improvement. It is likely that transplanted cells release neurotransmitters or neurotrophic/neuroprotective factors which counteract degeneration or promote regeneration. Even transplanted glial cells have been used to modify response to injury and assist in structural repair and promote remyelination. Studies using bone marrow stromal cells or umbilical cord blood cells as potential donors have shown functional improvement in behavioral recovery in animal models within days of transplantation. This raises issues whether recovery observed in such short periods is related to release of trophic factors rather than engraftment and differentiation of transplanted cells into mature neurons and/or glia.²⁶⁻²⁹ The functional benefits after neural

transplantation are likely to be mediated by one of the following mechanisms²²:

1. Neurotransmitters released from the graft tissue act on the afferent deprived limb of the postsynaptic receptors.
2. Release of the neurotrophic/growth factors (brain derived neurotrophic factor [BDNF], glial derived neurotrophic factor [GDNF], nerve growth factor [NGF], etc., acting as local pumps to support cell function and to prevent cascade of apoptosis. Regenerating neuronal population further prevents subsequent cell death.
3. Reestablishment of local interneuronal connections and synaptic connectivity between the host and graft.
4. Cell differentiation and integration.
5. Improvement of regional oxygen tension.
6. Limit glial reaction and prevent retrograde degeneration.

Possibly, the overall success of functional outcome is mediated by a combination of the above mentioned factors.

Cell Types and Sources

A range of different cell types under investigation for transplantation in experimental and clinical stroke trials are N Tera Neuron like cells (NT2N), autologous bone marrow derived stem cells (BMSC), human umbilical cord blood cells, NSC, and adipose tissue cells.^{23,29}

Adult stem cell therapy for stroke can be divided in an endogenous and exogenous approach. The aim of the endogenous stem cell therapy is to exploit the population of adult stem cells already physiologically present either in the central nervous system (CNS) or hematopoietic system derived adult stem or precursor cells are administered locally or systemically after purification and propagation in culture.^{23,30,31}

Interestingly, acute cerebral ischemia in human individuals leads spontaneously to a three-fold increase in CD34+ cell count in the peripheral blood. Considering this change as an insufficient self-repair mechanism, it is a logical consequence to further promote CD34+ cell mobilization pharmacologically by the administration of granulocyte-colony stimulating factor (G-CSF). In addition, G-CSF has been described to exert neuroprotective effects following cerebral ischemia. A recent preclinical study found functional improvement in rats with focal G-CSF. There are ongoing clinical studies with G-CSF in acute ischemic stroke.^{23,31,32}

Currently guidelines are being formulated to guide further research into the role of stem cell therapy in both translational and basic research areas.

Over the past decades, convincing evidence emerged that neurogenesis in the adult CNS is a continuous physiological process. Neurogenesis is present in two regions, the subventricular zone (SVZ) and the subgranular zone of the dentate gyrus. Additionally, recent studies also indicated the existence of NSCs in other regions of the CNS, namely, the striatum, spinal cord, and neocortex. External global stimulants, such as enriched environment, physical activity and stress, or application of defined molecules, such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), BDNF, and erythropoietin

differentially modulate adult neurogenesis and have been tried in experimental models of stroke.³¹

Some of the major public sector tertiary care centers and institutes are presently conducting peer reviewed scientific studies on various aspects of stem cell therapy in stroke patients, as well as in animal models of stroke.

Another study recently completed under the aegis of department of science and technology of India (DST; Padma et al) found benefit with autologous bone marrow derived and expanded marrow stromal cells infusion given intravenously in patients with chronic stroke (3 months to 2 years after the event). The autologous bone marrow derived mononuclear cells and ex vivo culture expanded mesenchymal stem cells were found to be safe and feasible mode of treatment in chronic stroke in their study of 40 patients.³³⁻³⁵ Combining physiotherapy with autologous stem cells (mononuclear cells and mesenchymal stem cells) lead to clinical and functional improvements as assessed on functional MRI (fMRI) and diffusion tensor imaging (DTI) and the lasting effects of the same could be observed till 24 weeks. The administration of stem cells lead to cortical reorganization as evidenced by measurement of laterality index (LI), fractional anisotropy ratios (FA), and signal intensity change of the activated hemisphere and the fiber tract density and length on fMRI and DTI studies.³⁶

Translation to the Clinic

The essential difference between neuroprotective and neurorestorative treatments is that the former treat the lesion and the latter, whether they are cell based or pharmacological therapies treat the intact tissue. The therapeutic time window and treatment protocols will thus be very different.²⁰ Restorative therapies are effective when initiated 1 month after stroke onset and cerebral perfusion is not problematic because the therapeutic target is cerebral tissue with normal perfusion. Restorative treatments are expected to reduce some of the impediments to the translation of laboratory proven therapies to patients. However, restorative treatments have their own sets of complicating factors. The treatments must be clearly proven to be safe in patients; this is particularly challenging for cell-based therapies. The interactions between restorative interventions and different environments, comorbidities, and rehabilitations strategies must be taken into account.^{19,20,37}

Role of Growth Factors in Post Stroke Recovery

Neurotrophic Agents and Growth Factors

Basic FGF was shown to protect against excitatory amino acid toxicity in vitro, basic FGF chimeric peptide was highly effective in reducing infarct volume in a rodent model of permanent focal ischemia. FGF has been investigated in phase II/III trials. The results of the Clinical Safety Trial of Intravenous Basic FGF in Acute Stroke did not report any serious adverse events. The European-Australian phase II/III safety and efficacy trials were halted; no significant improvement was noted, although a trend toward treatment advantage was observed with the agent.³⁸

Angiogenesis is the key feature of neuronal post-stroke reorganization and stroke recovery. Brain ischemia itself induces angiogenesis through hypoxia inducible factor 1. A transcription factor that responds to the changing intracellular O₂ concentration and induces erythropoietin expression. Angiogenesis is activated through release of polypeptide growth factors and cytokines and specific up-regulation of the angiogenic factors involves transforming growth factor β , platelet derived growth factor, VEGF and basic FGF-2 in response to ischemia. VEGF is the postpotent hypoxia inducible angiogenic factor amongst all and is secreted by endothelial cells and pericytes. VEGF is upregulated by other growth factors within hours of stroke and has a strong influence on growth of new blood vessels in the injured areas of the brain. Its production constitutes adaptive response to hypoxia which promotes angiogenesis in poststroke events and eventually leads to functional recovery.^{39,40}

Role of VEGF in Postischemic Stroke Recovery

Endogenous VEGF

In the ischemic brain, the macrophages, neurons, and glial cells appear to contain VEGF. Many cytokines and growth factors have been shown to modulate VEGF gene expression. Erythropoietin (EPO) plays an important role in angiogenesis through upregulation of VEGF/VEGF receptor system, both directly by enhancing neovascularization and indirectly by recruiting endothelial progenitor cells (EPCs).³⁸

Exogenous VEGF

Hypoxia itself induces an increase of VEGF expression in ischemic area of brain but this endogenous VEGF secretion is inadequate to entirely protect the brain injury. In humans, expression of VEGF was found to be significantly increased after AIS. VEGF reached a peak 7 days after stroke and remained elevated up to 14 days. Mean VEGF expression was lowest in serum of patients with small infarct, increased in moderate infarct, and was greatest in large infarct. Serum VEGF levels also correlated with the long-term prognosis in AIS. Elevated VEGF levels were found proportional to improved NIHSS scores after 3 months.³⁸

Exercise and VEGF

Exercise induces neurogenesis and angiogenesis through growth factors cascade. Endurance exercise, that is, running up regulates BDNF and synapsin one mRNA which helps to facilitate better outcome in patients with stroke. Exercise also strengthens the micro vascular integrity after cerebral ischemia and upregulates endothelial nitric oxide (NO) synthesis which improves endothelium function again up regulating VEGF expression.³⁸

Repetitive Transcranial Magnetic Stimulation and VEGF

The repetitive transcranial magnetic stimulation (rTMS) has been known to upregulate neurotrophins like VEGF. The purpose of the study was to investigate the effect of

high-frequency rTMS with constrain-induced movement therapy (CIMT) on serum VEGF level in chronic stroke patients with upper extremity motor deficits. The ongoing RCT recruited 35 chronic stroke patients from 3 to 18 months of index event with Brunnstrom's stages 2 to 4 and NIHSS of 4 to 20. Patients were randomized to CIMT alone and rTMS with CIMT. The rTMS (10 Hz, 750 pulses with 110% RMT) was administered for 3 weeks (5 days/week). Serum level for VEGF was estimated along with assessment of Fugl Meyer (FM), Barthel's index (BI), and modified Rankin's scales at base line; 15th and 90th day. Significant improvement was seen in patients treated with rTMS with physiotherapy on FM (50.25 vs. 40.9; $p = 0.001$) and BI (89.38 vs. 77.86; $p = 0.001$). VEGF levels were upregulated (845.51 vs. 450.07 pg/mL) in the combination group as compared with only physiotherapy group. A positive correlation of VEGF with FM score ($r = 1$) was observed in the combination group. Increased serum VEGF after rTMS may help in enhancing neuroplasticity leading to significant improvement in upper extremity motor function.⁴¹⁻⁴³

Pharmacotherapy for Neurointervention

Role of Nitric Oxide

Nitric oxide (NO) received attention when it was discovered that endothelial derived relaxing factor was in fact NO, an integral molecule involved with maintaining endothelial cell integrity, as well as participating, in hemodynamic homeostasis. The administration of NO donors increases neurogenesis in the adult rat SVZ and dentate gyrus suggesting an expanded role for the NO cascade beyond embryogenesis. Treatment with NO donors beginning 24 hours poststroke in rat models is associated with increased neurogenesis and improvement in functional outcome despite no change in infarct volume.^{44,45}

Phosphodiesterase Inhibitors

The cGMP levels may be increased by inhibiting its metabolism by the phosphodiesterase enzyme. The strategy of increasing the downstream mediator cGMP without affecting NO levels may be preferred due to the mixed outcomes in stroke reported in animal models. A major phosphodiesterase 5 inhibitor is sildenafil. Animals treated with sildenafil poststroke achieved significant and substantial increase in neurological functional recovery. Sildenafil demonstrated improved cerebral blood flow, neurogenesis, angiogenesis and synaptogenesis following experimental stroke, even when therapy is delayed for up to 1 week. In these studies, once again, the improvements in functional outcome that occur despite no change in infarct volume are intriguing.^{46,47}

Statins

Drugs which increase high-density lipoproteins, such as slow release niacin have also been employed to treat stroke and have shown substantial neurological benefit when treatment is initiated days after stroke. Other neurorestorative agents

under investigation are erythropoietin, carbamylated EPO, and Thymosin B4.²¹

Role of Gamma-Aminobutyric Acid

Recovery after stroke involves remapping of the neuronal circuitry in the regions adjacent to the site of injury or the peri-infarct zone. A pharmacological approach to reestablish functional neuronal connections that are lost during stroke could enhance current physical rehabilitation therapies. Recently Clarkson showed that inhibiting tonic gamma-aminobutyric acid (GABA) ergic signaling days after stroke can improve locomotor function, suggesting a therapeutic approach that is less sensitive than acute reperfusion therapies. GABA signaling reduces neuronal excitability and thereby modulates synaptic plasticity.⁴⁸

Role of Minocycline

Minocycline is the second generation tetracycline derivative known to have anti-inflammatory effects independent of its antimicrobial action. Recent studies have shown that minocycline prevents microglial activation, and also has notable beneficial effects in animal models of global and transient focal cerebral ischemia and other brain injuries. The proposed mechanisms of minocycline include anti-inflammatory effects, reduction of microglial activation, MMP reduction, NO production, and inhibition of apoptotic cell death. In a randomized single-blinded study, we studied the effects of oral minocycline (200 mg/day) for 5 days poststroke versus placebo. Of 50 patients included into the trial, patients who received minocycline had significant improvements in stroke outcome as noted on NIHSS, mBI, and MRS scores. Larger trials are needed for confirming these results.⁴⁹

Role of EPO

Recombinant EPO was reported to be safe and efficacious in a proof of concept study. A phase II/III study of 522 patients, however, was negative and showed a higher death rate and complications in patients receiving EPO. Possible interaction with rTPA was cited as a likely cause of increased mortality.^{21,50-52}

Role of G-CSF

An IV G-CSF has also been investigated in a dose escalation phase IIa study (AXIS: 44 patients, dose administered within 12 hours). The authors reported a good tolerability and suggest further trials.⁵¹

Role of Cerebrolysin

Cerebrolysin, a peptide based drug is another candidate with potential for approval to be used as a restorative agent. Multiple laboratories have demonstrated the safety and efficacy of this drug in the treatment of experimental stroke. Cerebrolysin is currently in clinical trials and also in use in some countries for clinical treatment of stroke. Cerebrolysin has been proposed to induce neurogenesis, and angiogenesis in animal models of stroke and concomitantly enhances brain plasticity and recovery after stroke.²¹

NIASPAN Treatment Promotes Brain Plasticity after Stroke

There is growing body of evidence that strengthens the link between brain high-density lipoprotein cholesterol (HDL-C) metabolism and factors involved in synaptic plasticity. Scavenger receptor class B1 binds HDL and facilitates α -tocopherol and cholesteryl esters transfer into cells from circulating HDL. Niaspan, an extended release formulation of Niacin, may be effective in reducing neurological deficits poststroke by promoting axonal remodeling, angiogenesis, and arteriogenesis. Niaspan when administered 24 hours after MACo significantly upregulates neuronal synaptic rewiring in the perinfarct region and restores connections between different cerebral areas after stroke. This increase in axonal density and synapse formation translates into long-term functional recovery after experimental stroke. Niacin induced increase in synaptic plasticity and axon growth may be mediated by the upregulation in the BDNF-TrkB (tropokin receptor kinase B) axis.^{19,53}

Enhancing Recovery with Special Reference to Walking and Aphasia after Stroke

Motor weakness and the ability to walk have been the primary targets for testing interventions that may improve after stroke. Physical therapeutic interventions enhance recovery after stroke; however, the timing, duration, and type of intervention require clarification and further trials. Pharmacotherapy, in particular with dopaminergic and selective serotonin-reuptake inhibitors, shows promise in enhancing motor recovery after stroke; however, further large scale trials are required.⁵⁴

Pharmacotherapy may influence how the injured brain recovers. This complex array of influences and recent research increasingly confirm this concept. Many varied strategies and techniques are undergoing assessment including pharmacological therapy for aphasia, transcranial magnetic stimulation for motor recovery, and cognitive rehabilitation for attention deficits.⁵⁵ It is possible that when used in combination, these techniques may be symbiotic and synergistic. Much of the research in the area of stroke has focused on recovery of walking. Walking is a basic human function, often affected by stroke, more easily observed, more easily measured, and potentially more easily rehabilitated than other functional deficits.^{55,56}

Besides loss of power in lower limb, walking also relies on the integrity of the trunk for balance, and the upper extremity for associated walking movements. In addition to motor weakness, the complex activity of walking requires the integration of sensory, visual, perceptual, and cognitive inputs.⁵⁷

Giacino et al randomized patients with severe traumatic brain injury to amantadine, an indirect dopamine agonist, or placebo between 4 and 16 weeks after injury. Patients were treated for 4 weeks and then assessed at 6 weeks. Amantadine increased the speed of recovery during the active treatment phase. Although the Disability Rating Scale (DRS) between

baseline and at 6 weeks was similar in both groups, a post hoc analysis at the end of 4 weeks of treatment showed that more patients on amantadine had an improvement in their Disability Rating Scale scores and categories. It would now seem that another pharmacological intervention changes the course of “natural” recovery after brain injury.⁵⁸

Dopaminergic agents and selective serotonin-reuptake inhibitors (SSRIs) have to date shown the most promise in altering the natural history of recovery after stroke.⁵⁹ Dopamine is a neurotransmitter that may promote neuroplasticity in the cerebral cortex and that may also be important in working memory and learning.^{60,61} Animal studies suggest that dopamine is an important neurotransmitter for learning and memory.⁶² A single-oral dose of 100 mg of levodopa and 25 mg of carbidopa can enhance the ability of patients with chronic stroke to encode an elementary motor function. Scheidtmann et al randomized 53 patients between 3 weeks and 6 months poststroke to either 3 weeks of 100 mg of levodopa with carbidopa or placebo daily, 5 days per week before physiotherapy. Patients who received levodopa had a significant improvement in motor recovery and in particular many more achieved the ability to walk early and independently. Subsequent small studies using levodopa with or without methylphenidate or levodopa with or without amphetamine could not show a difference in motor recovery or improvement in functional outcomes with treatment.⁶³ An ongoing study started in 2010, enrolling 572 patients, with a new stroke who cannot walk 10 m, were to receive 100 mg of levodopa and 25 mg of carbidopa, or placebo, 1 hour before physiotherapy. Patients will be treated for a maximum of 6 weeks. The primary outcome will assess the number of patients walking independently at 8 weeks after randomization.⁶⁴

SSRIs are essential for regulation and maintenance of memory, mood, and sleep. They have also been implicated in modulating neuronal plasticity. Animal studies suggest that SSRIs may be involved in neurogenesis and activation of cortical motor areas. A single dose of citalopram can normalize the balance in cortical excitability, as measured by transcranial magnetic stimulation, of the affected as compared with the unaffected hemisphere in stroke patients.⁶⁵ Patients more than 6 months after stroke, in a single-dose crossover experiment with citalopram, showed improved hand dexterity as measured by the nine-hole peg test, while using the affected hand. A single dose of fluoxetine given to patients, 2 to 3 weeks after stroke showed improved motor skills on the none-hole peg test, and increased activation of the affected side on functional resonance imaging.⁶⁶

The above studies demonstrate that SSRIs alter motor recovery and motor function. Chollet et al randomized 118 acute ischemic stroke patients within 5 to 10 days of stroke to fluoxetine (20 mg/day by mouth) or placebo. At the end of 90 days of treatment, patients were assessed using the Fugl-Meyer motor scale (motor score varies from 0 to 100, 66 points upper limb, 34 points lower limb; movements measured as none, partial, or full). The mean improvement in the total Fugl-Meyer motor scale from baseline to 90 days was significantly higher in those patients treated with fluoxetine. The improvement was present both in the arm and the leg. Patients treated with fluoxetine were more likely to

reach functional independence as measured by the modified Rankin's scale.⁶⁷ A recent meta-analysis of randomized controlled trials that recruited stroke patients treated with an SSRI compared with usual care or placebo identified 52 trials for analysis. Although the use of SSRIs seems to be associated with an improvement in dependence, disability, neurological impairment, and depression, methodological limitations call for large randomized trials to derive definitive conclusions.⁶⁸

Neurorestorative Therapy using Pharmacotherapy: Is There a Hope?

Is pharmacological restorative therapy poststroke merely a chimera? A perusal of clinical trials of neurorestorative agents certainly seem depressing at first glance. Nevertheless, if experimental evidence of neurorestoration is definite, why then has it not been replicated in clinical domains?

Translation of these restorative agents from the laboratory to the clinic has to be performed with caution and care, failing which the bench to bed-side transition will be a failure, like it happened on several previous occasions. For example, EPO was demonstrated in multiple preclinical studies to provide potent therapeutic benefit for the treatment of stroke and appeared to be a strong candidate for translation into the clinic. The phase-III clinical trial that was performed was unsuccessful and had to be terminated because of high mortality and adverse events. Of the stroke patients in the reported trial, 63.4% were administered rTPA yet prior to the performance of the clinical trial, EPO was not tested in the laboratory in conjunction with rTPA. A subsequent study with the combination of EPO with rTPA clearly demonstrated in animals the adverse events observed in the clinical trial.

Criticisms of animal studies include the following: (1) small sample size (underpowered), (2) lack of randomization, (3) variable injury levels, (4) interspecies variations, (5) confounding variables (hypothermia and use of anesthetic agents), (6) lack of evaluation of the dose–response relationship and side-effects (therapeutic index), (7) inadequate outcome measures or biomarker end-points, and (8) flawed statistical analysis. On the basis of these observations, the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations were developed for providing a stronger preclinical database for potential therapeutic agents.⁶⁹

Role of Robotics

As demonstrated by two recently published clinical trials, the key to improve rehabilitation outcomes might be found in new assistive technologies, such as robotic exoskeletons and brain-machine interfaces.^{70,71}

In the first study, published in *Lancet Neurology* this year, Verena et al describe how the ARM in exoskeleton can facilitate the rehabilitation of hemiparesis caused by stroke.⁷² Therapy robotics have the potential to enhance recovery of a paralyzed arm or leg beyond what seems to be possible with conventional therapies. Myoelectric computer interface (MCI) is another technique being developed.

Machines assisting recovery from stroke (MARS) is a rehabilitation engineering research center in the United States which is also developing several assistive devices which have potential to enhance recovery with different exercise regimes.

Neurorestoration is a concept that has been proven emphatically in several experimental models of stroke. The lack of proof in clinical settings will continue to be discouraging until the reasons for failure in this endeavor are examined. The trials of the past cannot be termed as failures as they definitely have contributed to our understanding of the complex biology of brain injury. This knowledge must provide an impetus for the development of superior candidate molecules and methodological interventions that will enhance drug development, as well as clinical testing.

Note

The author was selected for Dr. Baldev Singh Oration for the year 2017-2018.

Conflict of Interest

None declared.

References

- 1 Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. *Pathophysiology* 2010;17(3):197-218
- 2 Cramer SC, Cassidy JM Application of fMRI to monitor motor rehabilitation In: Filippi M, ed. *fMRI Techniques and Protocols* New York, NY: Humana Press; 2016:833-849
- 3 Cramer SC. The EXCITE trial: a major step forward for restorative therapies in stroke. *Stroke* 2007;38(7):2204-2205
- 4 Cramer SC. Treatments to promote neural repair after stroke. *J. Stroke* 2018;20(1):57-70
- 5 Srivastava MVP. Restorative therapies after stroke: drugs, devices and robotics. *Ann Natl Acad Med Sci* 2017;53(1):51-65
- 6 Srivastava MVP, Bhasin A, Talwar T, Moonis M. Pharmacological agents in post stroke recovery. *J Neurol Stroke* 2014;1(6):00040
- 7 Wahl AS, Schwab ME. Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment. *Front Hum Neurosci* 2014;8(381):381
- 8 Rogalewski A, Schneider A, Ringelstein EB, Schäbitz WR. Toward a multimodal neuroprotective treatment of stroke. *Stroke* 2006;37(4):1129-1136
- 9 Belayev L. Overcoming barriers to translation from experimental stroke models In: Lapchak PA, Zhang JH, eds *Translational Stroke Research*. New York, NY: Springer 2012:471-492
- 10 Padma V, Fisher M, Moonis M. Thrombolytic therapy for acute ischemic stroke: 3 h and beyond. *Expert Rev Neurother* 2005;5(2):223-233
- 11 Padma S, Majaz M. Intra-arterial versus intra-venous thrombolysis within and after the first 3 hours of stroke onset. *Arch Med Sci* 2010;6(3):303-315
- 12 Molina CA, Saver JL. Extending reperfusion therapy for acute ischemic stroke: emerging pharmacological, mechanical, and imaging strategies. *Stroke* 2005;36(10):2311-2320
- 13 Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. *Stroke* 2010;41(9):1996-2000
- 14 Saver JL. Improving reperfusion therapy for acute ischaemic stroke. *J Thromb Haemost* 2011;9(1, Suppl 1):333-343
- 15 Berkhemer OA, Fransen PS, Beumer D, et al. MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372(1):11-20
- 16 Smith WS, Yan B. REVASCAT trial: further advancement in endovascular stroke therapy. *Stroke* 2015;46(10):3012-3013
- 17 Padma Srivastava MV. Management of stroke: the triumphs and the travails. *Neurol India* 2016;64(7, Suppl):S6-S7
- 18 Hill MD, Goyal M, Demchuk AM. Endovascular stroke therapy—a new era. *Int J. Stroke* 2015;10(3):278-279
- 19 Chen J, Venkat P, Zacharek A, Chopp M. Neurorestorative therapy for stroke. *Front Hum Neurosci* 2014;8:382
- 20 Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. *Lancet Neurol* 2009;8(5):491-500
- 21 Padma Srivastava MV, Bhasin A. Restorative therapy in stroke. *J Transplant Technol Res* 2014;4(2):136
- 22 Padma Srivastava MV. Restorative therapy in stroke using stem cells. *Neurol India* 2009;57(4):381-386
- 23 Savitz SI, Dinsmore JH, Wechsler LR, Rosenbaum DM, Caplan LR. Cell therapy for stroke. *NeuroRx* 2004;1(4):406-414
- 24 Okano H. Stem cell biology of the central nervous system. *J. Neurosci Res* 2002;69(6):698-707
- 25 National Institute of Health. Stem cell basics. Available at: <https://stemcells.nih.gov/info/basics/1.htm>. Accessed September 10, 2019
- 26 Zivin JA. Cell transplant therapy for stroke: hope or hype. *Neurology* 2000;55(4):467
- 27 Savitz SI, Rosenbaum DM, Dinsmore JH, Wechsler LR, Caplan LR. Cell transplantation for stroke. *Ann Neurol* 2002;52(3):266-275
- 28 Björklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. *Nat Neurosci* 2000;3(6):537-544
- 29 Isacson O, Deacon T. Neural transplantation studies reveal the brain's capacity for continuous reconstruction. *Trends Neurosci* 1997;20(10):477-482
- 30 Bliss T, Guzman R, Daadi M, Steinberg GK. Cell transplantation therapy for stroke. *Stroke* 2007;38(2, Suppl):817-826
- 31 Haas S, Weidner N, Winkler J. Adult stem cell therapy in stroke. *Curr Opin Neurol* 2005;18(1):59-64
- 32 Prasad K, Kumar A, Sahu JK, et al. Mobilization of stem cells using G-CSF for acute ischemic stroke: a randomized controlled pilot study. *Stroke Res Treat* 2011;2011:283473
- 33 Srivastava MVP, Bhasin A, Mohanty S, et al. Restorative therapy using autologous bone marrow derived mononuclear cells infusion intra-arterially in patients with cerebral palsy: An open label feasibility study. *Neurol Asia* 2011;16(3):231-239
- 34 Bhasin A, Srivastava MV, Kumaran SS, et al. Autologous mesenchymal stem cells in chronic stroke. *Cerebrovasc Dis Extra* 2011;1(1):93-104
- 35 Bhasin A, Srivastava M, Bhatia R, Mohanty S, Kumaran S, Bose S. Autologous intravenous mononuclear stem cell therapy in chronic ischemic stroke. *J Stem Cells Regen Med* 2012;8(3):181-189
- 36 Bhasin A, Padma Srivastava MV, Kumaran SS, Bhatia R, Mohanty S. Neural interface of mirror therapy in chronic stroke patients: a functional magnetic resonance imaging study. *Neurol India* 2012;60(6):570-576
- 37 Nishino H, Borlongan CV. Restoration of function by neural transplantation in the ischemic brain. *Prog Brain Res* 2000;127:461-476
- 38 Bogousslavsky J, Victor SJ, Salinas EO, et al. European-Australian Fibrinolytic (Trafermin) in Acute Stroke Group. Fibrinolytic (trafermin) in acute stroke: results of the European-Australian phase II/III safety and efficacy trial. *Cerebrovasc Dis* 2002;14(3, 4):239-251

- 39 Talwar T, Srivastava MVP. Role of vascular endothelial growth factor and other growth factors in post-stroke recovery. *Ann Indian Acad Neurol* 2014;17(1):1–6
- 40 Ucuzian AA, Gassman AA, East AT, Greisler HP. Molecular mediators of angiogenesis. *J Burn Care Res* 2010;31(1):158–175
- 41 Sharma H, Srivastava MVP, Bhatia R, Kumar N, Moganty R. Does vascular endothelial growth factor (VEGF) expression in combination with physiotherapy with/without repetitive transcranial magnetic stimulation (rTMS) play the role in acute stroke recovery? *Brain Stimul* 2015;8(2):324
- 42 Kubis N. Non-invasive brain stimulation to enhance post-stroke recovery. *Front Neural Circuits* 2016;10:56
- 43 Kuthiala N, Srivastava MVP. Is the change in serum vascular endothelial growth factor (Vegf) after high frequency rTMS in chronic stroke indicative of neuroplasticity? *Int J Stroke* 2016;11(3S):228
- 44 Zhang R, Zhang L, Zhang Z, et al. A nitric oxide donor induces neurogenesis and reduces functional deficits after stroke in rats. *Ann Neurol* 2001;50(5):602–611
- 45 Bauer V, Sotníková R. Nitric oxide–the endothelium-derived relaxing factor and its role in endothelial functions. *Gen Physiol Biophys* 2010;29(4):319–340
- 46 Bednar MM. The role of sildenafil in the treatment of stroke. *Curr Opin Investig. Drugs* 2008;9(7):754–759
- 47 Zhang R, Wang Y, Zhang L, et al. Sildenafil (Viagra) induces neurogenesis and promotes functional recovery after stroke in rats. *Stroke* 2002;33(11):2675–2680
- 48 Clarkson AN. Perisynaptic GABA receptors: the overzealous protector. *Adv Pharmacol Sci* 2012;2012:708428
- 49 Padma Srivastava MV, Bhasin A, Bhatia R, et al. Efficacy of minocycline in acute ischemic stroke: a single-blinded, placebo-controlled trial. *Neurol India* 2012;60(1):23–28
- 50 Ehrenreich H, Hasselblatt M, Dembowski C, et al. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol Med* 2002;8(8):495–505
- 51 Schäbitz WR, Laage R, Vogt G, et al. AXIS: a trial of intravenous granulocyte colony-stimulating factor in acute ischemic stroke. *Stroke* 2010;41(11):2545–2551
- 52 Ehrenreich H, Weissenborn K, Prange H, et al. EPO Stroke Trial Group. Recombinant human erythropoietin in the treatment of acute ischemic stroke. *Stroke* 2009;40(12):e647–e656
- 53 Cui X, Chopp M, Zacharek A, et al. Niacin treatment of stroke increases synaptic plasticity and axon growth in rats. *Stroke* 2010;41(9):2044–2049
- 54 Greener J, Enderby P, Whurr R. Pharmacological treatment for aphasia following stroke. *Cochrane Database Syst Rev* 2001
- 55 Rösser N, Flöel A. Pharmacological enhancement of motor recovery in subacute and chronic stroke. *NeuroRehabilitation* 2008;23(1):95–103
- 56 Hsu WY, Cheng CH, Liao KK, Lee IH, Lin YY. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. *Stroke* 2012;43(7):1849–1857
- 57 Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet* 2011;377(9778):1693–1702
- 58 Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med* 2012;366(9):819–826
- 59 Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience* 2002;111(4):815–835
- 60 Berends HI, Nijlant JM, Movig KL, Van Putten MJ, Jannink MJ, Ijzerman MJ. The clinical use of drugs influencing neurotransmitters in the brain to promote motor recovery after stroke; a Cochrane systematic review. *Eur J Phys Rehabil Med* 2009;45(4):621–630
- 61 Floel A, Hummel F, Breitenstein C, Knecht S, Cohen LG. Dopaminergic effects on encoding of a motor memory in chronic stroke. *Neurology* 2005;65(3):472–474
- 62 Acler M, Robol E, Fiaschi A, Manganotti P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. *J Neurol* 2009;256(7):1152–1158
- 63 Scheidtmann K, Fries W, Müller F, Koenig E. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. *Lancet* 2001;358(9284):787–790
- 64 Bhakta BB, Hartley S, Holloway I, et al. The DARS (Dopamine Augmented Rehabilitation in Stroke) trial: protocol for a randomised controlled trial of Co-careldopa treatment in addition to routine NHS occupational and physical therapy after stroke. *Trials* 2014;15:316
- 65 Zittel S, Weiller C, Liepert J. Citalopram improves dexterity in chronic stroke patients. *Neurorehabil Neural Repair* 2008;22(3):311–314
- 66 Pariante J, Loubinoux I, Carel C, et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. *Ann Neurol* 2001;50(6):718–729
- 67 Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol* 2011;10(2):123–130
- 68 Mead GE, Hsieh CF, Lee R, Kutlubaev MA, Claxton A, Hankey GJ, Hackett ML. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev* 2012;11:CD009286. Doi: 10.1002/14651858.CD0
- 69 Reis C, Akyol O, Ho WM, et al. Phase I and phase II therapies for acute ischemic stroke: an update on currently studied drugs in clinical research. *BioMed Res Int* 2017;2017:4863079
- 70 Poli P, Morone G, Rosati G, Masiero S. Robotic technologies and rehabilitation: new tools for stroke patients' therapy. *BioMed Res Int* 2013;2013:153872
- 71 Frisoli A, Solazzi M, Loconsole C, Barsotti M. New generation emerging technologies for neurorehabilitation and motor assistance. *Acta Myol* 2016;35(3):141–144
- 72 Klamroth-Marganska V, Blanco J, Campen K. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. *Lancet Neurol* 2014;13(2):159–166