



Editorial

Clinical Aspects of Stroke Cell-based Therapy: Current Status and Future Perspectives

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“There is no incurable disease – only the lack of will.” Avicenna

In spite of progress made in stroke treatment in recent years, no assured treatment for complete recovery of patients has been introduced. Considering remarkable social and economic burden of stroke care, finding efficient methods for functional recovery is crucial. In this regard, evidence indicates that stem cell-based therapy could be a promising tool for the restoration of injured brain function. Stem cells exert their neuroprotective effects through anti-inflammatory and growth factors secretion as well as through replacing lost neurons in host tissue [1]. Stem cell therapy can be carried out by activating endogenous stem cells to generate new neurons or by transplantation of exogenous stem cells. Fortunately, exogenous stem cell transplantation has been found safe in human trials along with indicating some grades of recovery in chronic stroke patients [2].

The main routes for stem cells implantation are divided into intracerebral, intra-arterial, and intravenous. Each of these routes has its own benefits and shortcomings. The intracerebral route has a higher probability of transplanted cell integration after accurate implantation to an infarcted or peri-infarcted area. However, as this approach is invasive, it can be performed in chronic stroke cases but not in acute stroke cases because of the risk of hemorrhage; utilizing biomaterials could be a reliable support for cellular survival after intracerebral engraftment of cells into host tissue. The intra-arterial route is less invasive

than the intracerebral route; however, the probability of vascular obstruction or the generation of micro-emboli is possible. As lower rate of transplanted cell engraftment in the intra-arterial approach occurs, enhancing extravascular activity would be advantageous. Beneficially, this route can be combined with post-stroke intra-arterial mechanical thrombectomy. Last, the intravenous route is widely used for cell injection in clinical trials, which is non-invasive as well as effective. However, due to cell trapping before reaching its destination, its efficacy is lower than other routes [3].

Based on information retrieved from the US NLM Clinical Trials database [URL: <https://clinicaltrials.gov/ct2/results?cond=Stroke+stem+cells&term=&cntry=&state=&city=&dist=26> July, 2018], 52 trials were registered for stem cell intervention in the field of stroke therapy. Many of these trials are Phase 1 or Phase 2. Two registered clinical trials are Phase 3 [NCT01716481 and NCT03545607]. However, the range of participants is wide (2-300). Three trials are utilizing the human neural stem cells (NSC) line for transplantation to chronic ischemic stroke patients (NCT01151124, NCT02117635, and NCT03296618). A notable indicator in stem-cell-based therapy is lack of immunologic or cellular adverse events; functional neurological recovery in clinical trials was analyzed based on standard scales such as the National Institutes of Health Stroke Scale (NIHSS), the European Stroke Scale, the Fugl-Meyer Scale, and the Rankin Scale. Accordingly, in a Phase 1 study, transplantation of an immortalized NSC line (CTX, developed by ReNeuron Co.) to the ipsilateral putamen of patients with chronic ischemic stroke was performed. Two years follow up after injection demonstrated an average of a two-point reduction in the NIHSS score. The promising results of the abovementioned study in terms of safety and efficacy suggests additional experiments with CTX in patients [4]. Similar to NSC, no cell-therapy-related adverse events were observed and mutually neurological recovery was significant in the first Phase 1/2a intracerebral cell therapy of chronic ischemia in North America exerted by mesenchymal stem cells (MSC) transplantation [5]. In other studies, in spite of observed safety for the intravenous administration of multipotent

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adult progenitor cells [6], bone marrow mononuclear stem cells [7], and MSC [8], there was little or no significant stroke recovery in patients. This issue could be attributed to lower accessibility of injected cells to the injured area. Notably, the limitation of MSC for stroke therapy compared to NSC is that they are incapable of becoming functional after differentiating into neurons in host tissue [9]. This issue should be considered for targeting cell replacement as an approach for stroke cell therapy.

In addition to functional recovery scales, structural changes can be followed up by magnetic resonance imaging (MRI) and positron emission tomography (PET). These tools demonstrate injured area volume and metabolic activity [10, 11]. Multiparametric MRI could be an especially helpful tool for detecting cell-therapy effectiveness in clinical trials. Furthermore, revealing penumbra, which is weighty in humans compared to animals, PET is a valuable instrument for tracking activity of endogenous NSC in recovery [12, 13].

For future cell-therapy planning, human-induced pluripotent stem cells (iPSC) are often a typical choice for stem cell-based therapies as they are capable of differentiating into neuronal progenitor cells (NPC) [12]. Moreover, dental stem cells could be applicable as their merits are remarkable, such as easy approachability, possessing NSC characteristics (differentiable to functional neurons), neuroprotectivity, storability, and being ethically non-controversial [14]. In this regard, optimizing methods for cellular reprogramming and differentiation are fundamental for achieving safer as well as survivable and integrable cell products for repairing injured tissue.

Conclusively, stem cell-based therapies should be scrutinized for all aspects of tumorigenicity and their fate in host tissue in preclinical trials [13].

References

- Hankey GJ. Stroke. *The Lancet*. 2017;389(10069):641-54.
- Ward NS. Restoring brain function after stroke - bridging the gap between animals and humans. *Nat Rev Neurol*. 2017;13(4):244-55.
- Rodriguez-Frutos B, Otero-Ortega L, Gutierrez-Fernandez M, Fuentes B, Ramos-Cejudo J, Diez-Tejedor E. Stem Cell Therapy and Administration Routes After Stroke. *Transl Stroke Res*. 2016;7(5):378-87.
- Kalladka D, Sinden J, Pollock K, Haig C, McLean J, Smith W, et al. Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study. *Lancet (London, England)*. 2016;388(10046):787-96.
- Steinberg GK, Kondziolka D, Wechsler LR, Lunsford LD, Coburn ML, Billigen JB, et al. Clinical Outcomes of Transplanted Modified Bone Marrow-Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study. *Stroke*. 2016;47(7):1817-24.
- Hess DC, Wechsler LR, Clark WM, Savitz SI, Ford GA, Chiu D, et al. Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Neurology*. 2017;16(5):360-8.
- Prasad K, Sharma A, Garg A, Mohanty S, Bhatnagar S, Johri S, et al. Intravenous autologous bone marrow mononuclear stem cell therapy for ischemic stroke: a multicentric, randomized trial. *Stroke*. 2014;45(12):3618-24.
- Bang OY, Lee JS, Lee PH, Lee G. Autologous mesenchymal stem cell transplantation in stroke patients. *Ann Neurol*. 2005;57(6):874-82.
- Eckert MA, Vu Q, Xie K, Yu J, Liao W, Cramer SC, et al. Evidence for high translational potential of mesenchymal stromal cell therapy to improve recovery from ischemic stroke. *J Cereb Blood Flow Metab*. 2013;33(9):1322-34.
- Reis C, Akyol O, Ho WM, Araujo C, Huang L, Applegate R, II, et al. Phase I and Phase II Therapies for Acute Ischemic Stroke: An Update on Currently Studied Drugs in Clinical Research. *BioMed research international*. 2017;4863079.
- Wagenaar N, de Theije CGM, de Vries LS, Groenendaal F, Benders M, Nijboer CHA. Promoting neuroregeneration after perinatal arterial ischemic stroke: neurotrophic factors and mesenchymal stem cells. *Pediatric research*. 2018;83(1-2):372-84.
- Jendelova P, Kubinova S, Sandvig I, Erceg S, Sandvig A, Sykova E. Current developments in cell- and biomaterial-based approaches for stroke repair. *Expert opinion on biological therapy*. 2016;16(1):43-56.
- Sinden JD, Hicks C, Stroemer P, Vishnubhatla I, Corteling R. Human Neural Stem Cell Therapy for Chronic Ischemic Stroke: Charting Progress from Laboratory to Patients. *Stem Cells Dev*. 2017;26(13):933-47.
- Yalvac ME, Rizvanov AA, Kilic E, Sahin F, Mukhamedyarov MA, Islamov RR, et al. Potential role of dental stem cells in the cellular therapy of cerebral ischemia. *Curr Pharm Des*. 2009;15(33):3908-16.