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Current Update on Stroke Ischemic Management: Stem Cell as Emerging Therapy

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***Abstract*---*Stroke is one of the most important causes of morbidity and mortality worldwide, with survivors subjected to long-term disability. Stroke is classified as ischemic and hemorrhagic. 87 % of strokes are classified as ischemic. Except for thrombolytic therapy, there is no established treatment to reduce the neurological deficits caused by an ischemic stroke. Therefore, it is necessary to develop new therapeutic strategies designed to improve neurological functions after ischemic stroke. Stem cell-based therapies aim to promote neurogenesis and replacement of lost neurons or protect surviving neurons to improve neurological recovery. Further understanding of the mechanisms by which the stem cells exert their beneficial effect could potentially revolutionize the field. The next decade of stem cell research in stroke needs to focus on. Although still in need of exploration, stem cell treatments for stroke may offer ways to protect and replace neurons to improve outcomes for stroke patients.*
Keywords*---*clinical trial, emerging therapy, neuroregeneration, stem cell, stroke ischemic.

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Introduction

Stroke is a leading cause of mortality and morbidity and is estimated to cause > 5 million deaths per year throughout the world. Despite the recent advancement in therapeutic and rehabilitative strategies, stroke remains a major cause of financial burden on health resources worldwide (Bhatia et al., 2018). Ischemic strokes are caused by blockage of an artery in the brain, causing local hypoxia that damages brain tissue. Ischemic stroke represents 87% of total strokes in the US and is currently the main focus of stroke research (Barthels & Das, 2020; Maida et al., 2020; Wang et al., 2018). Although 80% of stroke patients survive for 1 year following the event, more than 70% have long-term disabilities (Steinberg et al., 2018).

Intravenous thrombolysis (IVT) administrated within 4.5 hours is the first-line treatment for acute ischemic stroke (Herpich & Rincon, 2020). However, only about one-third of patients with acute ischemic stroke have improved functional recovery using IVT (Du et al., 2021). Current treatments for ischemic and hemorrhagic strokes are restricted by their narrow time window and lack of regenerative benefits (Chrostek et al., 2019), so stem cell therapy is emerging as an ideal candidate for functional recovery in patients with stroke conditions (Wang et al., 2018).

Stem cell-based therapies for stroke offer a promising avenue because of their potential to address the unmet needs of stroke patients, providing neuroprotective and regenerative benefits (Mahla, 2016). Some stem cell populations have demonstrated the ability to modulate the immune system, and offer the promise of neuroprotective and neuroregenerative effects, enhancing the healing effects while mitigating inflammatory damage (Caplan & Correa, 2011).

Method

A literature search of Pubmed databases was performed to identify publications addressing topics about stem cells and management of stroke ischemic. The literature search was supplemented by relevant articles not included in our original search but identified from the review of referenced citations.

Result and Discussion

Pathophysiology of ischemic stroke

Brain ischemia is caused by an interruption of blood flow to the brain due to a clot and represents 87% of all stroke cases. Most of the strokes with ischemic origin are caused by atherosclerosis affecting the large artery and by embolism with cardiac genesis (Khikmatullaeva et al., 2021). Approximately 45% of ischemic strokes are provoked by a thrombus in a small or large artery whereas cardioembolic stroke accounts for 14–30% of all cerebral infarctions (Maida et al., 2020).

The occlusion of the cerebral artery results in a deficiency of oxygen, glucose, lipids, and consequently, in necrosis of the cerebral parenchyma. Multiple mechanisms, including excitotoxicity, oxidative stress, and inflammation, have been considered to explain the brain injury caused by ischemia (Maida et al., 2020). Oxidative stress and the triggering of the inflammatory process contribute to the rupture of the blood-brain barrier allowing activated blood-borne immune cells, such as neutrophils and T cells, to reach the cerebral parenchyma and accumulate in the tissue involved in ischemia (Tuttolomondo et al., 2015). As cells die and brain tissue is injured, molecular danger signals further increase phlogosis by activating more microglia and infiltrating leukocytes in a feed-forward response releasing more cytokines with proinflammatory action. The increased expression of cytokines further promotes the expression of adhesion molecules on endothelial cells that provokes additional recruitment of leukocytes from the peripheral blood (Maida et al., 2020). This process, which takes place after ischemia, leads to an increased neuronal cell death causing a larger infarcted area and a worse neurological outcome.

Stem cells in ischemic stroke

The initial goal of using stem cells to treat ischemic stroke was to regenerate the stroke-damaged tissue by cellular replacement. Stem cells can differentiate into all types of cells (Sayfullaevich, 2021). Exogenously administered cells appear to stimulate endogenous reparative processes and do not replace injured cerebral tissue (Shiber et al., 2010; Deb et al., 2010). It was once thought that intravenously administered cells would home in on the injured site and replace the dead neurons, but the current ideology for the use of these cells holds that these cells release many trophic factors like VEGF, IGF, BDNF, and tissue growth factors that stimulate brain plasticity and recovery

mechanisms. Upregulation of growth factors, prevention of ongoing cell death, and enhancement of synaptic connectivity between the host and graft are some of the common pathways through which intravenous stem cells work as "chaperones." Regarding the timing of transplantation, preclinical studies have shown that cell therapy increases functional recovery after acute sub-acute, and chronic stroke, but few studies have compared different time windows, with differing results according to the model system and cell type studied (Bliss et al., 2010).

Many types of stem cells have been tested and evaluated for their therapeutic potentials in the treatment of ischemic stroke, including mesenchymal stem cells (MSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), and induced pluripotent stem cell (iPS) (Tursunova et al., 2021). The majority of published studies explored the efficacy of transplantation of a single type of stem cells. Recently, several studies investigated the efficacy of transplantation of a combination of different stem cells (Conteduca et al., 2014).

Neural stem cells (NSCs)

Neural stem cells (NSCs) are theoretically the most appropriate cell candidates for neuro-restoration as they belong to the same tissue source and have a natural tendency to differentiate into neuronal cells. NSCs are multipotent cells that are generally found in the subgranular zone of the dentate gyrus of the hippocampus (Singh et al., 2020). Engraftment of NSCs has been reported to lead to the reformation of synaptic connections and improvement in the electrophysiological properties of mature neurons in the damaged brain (Oki et al., 2012). NSCs restore neuronal functions as they secrete several neurotrophic factors like BDNF and VEGF, which help in maintaining the health, generation, proliferation, and survival of the neurons, along with the maintenance of ECM (Smith et al., 2012). VEGF specifically helps in angiogenesis and vascular restoration of the blood vessels damaged due to ischemia. CNTF, GDNF, NGF, and other such factors secreted by NSCs also play vital roles in the protection, maintenance, and proliferation of neural cells (Singh et al., 2020).

Embryonic stem cells (ESCs)

Embryonic stem cells (ESCs) are pluripotent cells derived from the inner cell mass of the blastocyst. There have been a few studies where engraftment of murine ESCs in mouse models of ischemia has led to the restoration of behavioral deficits, synaptic connections, and damaged neurons. However, the use of ESCs in the clinical setting is argued against by many other groups due to their immunogenic nature and teratoma-forming tendency (Liu et al., 2014; Singh et al., 2020). Hence, scientists are now trying to establish the neuro-restorative ability of other stem cell types. One possible approach is to use in vitro pre-differentiated ESCs that become post-mitotic to minimize their tumorigenic potential (Liu et al., 2014). Neuronal precursors derived from human ESCs reduced infarct volume, increased neurogenesis, and improved behavioral outcome after distal MCAO in both young adult (3-month-old) and aged (24-month-old) rats (Jin et al., 2011).

Mesenchymal stem cells (MSCs)

Another type of cell with amazing neuro-restorative potential that has several other desirable properties, like being immunologically naive, easy to extract and maintain and expand in vitro, and not having associated ethical concerns, are mesenchymal stem cells (MSCs) (Russell et al., 2018). MSCs are multipotent stem cells that have their niche in body tissues like bone marrow, adipose tissue, umbilical cord, umbilical cord blood, dental pulp, etc (Russell et al., 2018; Singh et al., 2017). MSCs lead to neuro- restoration by one or more modes of action such as the release of paracrine factors, cell replacement, mitochondrial transfer, etc. MSCs also have an angiogenic effect. They have been reported to induce angiogenesis by the release of vascular endothelial growth factor (VEGF) (Shen et al., 2007). Adipose tissue-derived MSCs have proved to be equally effective in neuro-regeneration, with the added advantages of being easily accessible and more abundant (Singh et al., 2017). Adipose tissue-derived MSCs have been known to play a protective role through the release of extracellular vesicles. Studies are reporting the safety and efficacy of extracellular vesicles derived from adipose tissue-derived MSCs (Bang & Kim, 2019).

Induced pluripotent stem cells (iPSCs)

iPSCs were recently introduced as a potential cell source have been used as an appealing cell source for cell transplantation to repair neuronal networks disrupted by various CNS diseases, including ischemic stroke (Ito et al., 2012). iPSCs share similar features compared to ESCs in morphology, proliferative abilities, epigenetic status of

pluripotent cell-specific genes, and telomerase activity, but with the benefit that iPSCs can be produced from a patient's skin fibroblasts, thereby sparing the risk of immune rejection and ethical issues (Abe et al., 2012). iPSCs have the edge over other types of stem cells due to being non-immunogenic, easy to access, and non-interventional and not giving rise to ethical concerns. However, their generation is still an unresolved issue, as the reprogramming efficiency is still very low (Chang & Goldberg, 2012). Additionally, some studies have reported the formation of teratoma in the mouse brain, which implies that the tumorigenicity of iPSCs needs to be addressed and resolved before taking them into the clinical setting. iPSCs seem to be formidable stem cells for tissue regeneration (Singh et al., 2020).

Route of administration

Stem cell treatment after stroke has led to improvements in functional outcomes in preclinical studies. Intracerebral, intraventricular, subarachnoid, intra-arterial, intraperitoneal, intra- venous, and intranasal administration were the optimal routes for treatment. The most appropriate route, however, is still unknown. Below, we describe studies that have used a variety of routes or pathways to administer stem cell-based treatment (Timmers et al., 2008).

Intracerebral

One of the goals of transplanted exogenous stem cells was to reconstruct the cytoarchitecture of the damaged tissue after stroke. This therapy requires the survival of grafted cells in an inhospitable milieu including inflammation, cell death, and glial scar (Liu et al., 2014). It was initially thought that intracerebral administration was the best way for exogenous neural stem cells to reach the brain. These cells can self-renew and generate neural cells, which have been shown to have the ability to replace the neurons lost to stroke (Rosado-de-Castro et al., 2016). intracerebral administration showed implanted cells in the lesion size in comparison with other delivery routes because several million cells are transplanted into the brain and approximately 1/3 of the stem cells migrate toward the damaged regions as well as to the intact hemisphere (Darsalia et al., 2007). Several problems are associated with using the intracerebral or intraventricular route for stem cell administration for brain repair: invasiveness, poor cell availability, immune rejection, and an uncertain fate in the brain, which present hurdles to the translational application of cell therapy. To solve these matters, less invasive routes are promising candidates for cell-based therapy after stroke (Wu et al., 2015).

Intraarterial

The more common method of intra-arterial administration is to use catheterization to guide cells into the carotid artery, which prevents initial uptake by systemic organs to enable the delivery of large numbers of cells directly to the brain lesion (Gutiérrez-Fernández et al., 2011). However, even via the carotid artery, fewer exogenous cells (1–10 %) arrive at the lesion area, as expected. Administered stem cells have the potential to replace the lost neural connections, to produce and stimulate the release of trophic factors enhancing brain repair mechanisms. In recent years, several subtypes of cell therapies have been developed using the intra-arterial route in experimental animal models of stroke. Some studies have reported that intra- arterially administered neural stem cells are related to a successful recovery after stroke. These observations show that grafted cells do not need to be close to the damaged area to be effective (Rodríguez-Frutos et al., 2016). Microemboli have been reported in some cases; however, some studies report no adverse effects from the microemboli (Gutiérrez-Fernández et al., 2011). In addition, intra-arterial transplantation of autologous bone marrow mononuclear cells in nonacute ischemic stroke showed that cell transplantation is safe and feasible (Battistella et al., 2011).

Intra Venous

Many preclinical studies have obtained promising results after intravenous administration of cell-based therapy after stroke. Various types of cells and cell sources have demonstrated efficacy after stroke. Interestingly, comparing intravenous with intra-arterial routes shows both to be equally effective (Gutiérrez-Fernández et al., 2011). Bang et al. observed that intravenous infusion of autologous mesenchymal stem cells was a safe treatment that could improve neurological deficits, based on five patients with severe stroke (Bang et al., 2005). Another study was later performed to evaluate the safety and efficacy of autologous intravenous mesenchymal stem cell administration to a larger population and demonstrated that this treatment was safe for stroke patients based on 5 years of follow-up (Rodríguez-Frutos et al., 2016).

Current clinical trials

Currently, over 70 studies with known status are recorded at the clinicaltrials.gov website. About half of these studies have passed the phase I safety evaluation and entered the phase II efficacy test. MSCs are the Star stem cells for clinical studies. A large number of clinical trials provided evidence that intravenous injection of MSC is safe and feasible in humans (Bhasin et al., 2013). Intravenously injected autologous serum cultured MSCs into 12 ischemic patients greatly reduced infarct volume and neurobehavioral deficits after 1 week of MSCs transplantation, without teratoma formation in a 1-year follow-up (Honmou et al., 2011). In contrast to MSCs, other cell types, such as NPCs, have been less frequently studied in clinical studies. Two clinical trials have demonstrated that the injection of neuronal cells derived from a teratocarcinoma cell line is beneficial for stroke patients (Gautret et al., 2020). However, the sample size (4–7 patients per group) was too small to evaluate the therapeutic efficacy of NPC (Steinberg et al., 2016).

Although most clinical studies achieved promising data, it's noted that one trial was terminated after intracerebral transplantation of fetal porcine NPCs into five patients in light of significant side effects were observed in two patients. Another study demonstrated that intrathecal administration of cell suspensions from immature nervous and hematopoietic tissues has no side effects in 10 patients over 6-month observation (Rabinovich et al., 2005).

Conclusion

Better treatments for stroke remain a pressing, unmet need. Evolving evidence highlights the potential for stem cell therapies to treat stroke, but also demonstrates the challenges that must be overcome to achieve a consistent, efficacious treatment for patients. However, stem cell-based therapy is in its infancy. The mechanism of these strategies is not completely elucidated, and many hurdles need to be overcome before clinical application. We do not know which stem cell and the delivery route is the most effective for the cellular therapy, how many cells should be transplanted, where these cells travel, and what these cells eventually become if they do survive. Further understanding of the mechanisms by which the stem cells exert their beneficial effect could potentially revolutionize the field. The next decade of stem cell research in stroke needs to focus on. Although still in need of exploration, stem cell treatments for stroke may offer ways to protect and replace neurons to improve outcomes for stroke patients.

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