A Review on Stem Cells Therapy: A New Hope for Neonatal and Adult Brain Damage

Samiksha G. Dhanuskar, Dr. Karishma A. Nikose

Abstract: After neuronal cell injury, self-neuronal regeneration is frequently minimal or non-existent, necessitating the development of novel methods to cure neurological impairment. Review of the research on stem cell treatment for neurological conditions. Because of their ability to regenerate, stem cells have demonstrated promise in the treatment of a number of neurological conditions and impairments. Early clinical trials and animal models have shown encouraging outcomes from the transplantation or administration of many stem cell types. But there are still issues with their application. It is necessary to decide on the kind of stem cell to be utilized, the best way and route of administration, the quantity of stem cells given, preconditioning, and the injection schedule. For every neurological illness, the review summarizes the main conclusions from current, excellent research, going into cell production, distribution strategies and treatment results.

Although the review highlights the capacity of stem cells to directly rebuild brain circuits and replace missing neurons, it also highlights the crucial role that paracrine and immunomodulatory systems play in mediating the therapeutic benefits of stem cells in the majority of neurological illnesses. The essay also examines the difficulties and restrictions involved in implementing stem cell therapy in clinical settings, such as problems with cell source, scalability, safety and regulatory constraints.

Keywords: ***Stem Cell Tracking, Neonatal Brain Injury, Neurological Disorders, Routes of Administration, clinical Trials.***

INTRODUCTION

Despite its sophistication, the central nervous system remains complex and challenging to comprehend. Many abnormalities of the central nervous system can cause permanent deficits and are frequently connected with cognitive and physical disability[1].

Brain injuries are a global calamity. It remains a global health problem with few treatment options. Figure 1 displays elements of the brain[2].The medulla oblongata, cerebellum, and cerebrum make up the brain. Brain injuries are common.

Many patients frequently suffer from conditions like Parkinson's disease, stroke, and traumatic brain injury. In addition to causing physical problems, these illnesses might result in financial liabilities for an individual[3]. Research into gene therapy and other innovative technologies is hindered by the lack of viable treatment choices.

Therefore, research on stem cells is prioritized in order to lead the field of regenerative medicine. Future Neuro-regenerative powers are promised by this treatment. From table to in vitro, they support the initiation of clinical research methodologies, possible cure combinations, and ethical protocols. The percentage of human brain injury is displayed in the figure below[4].

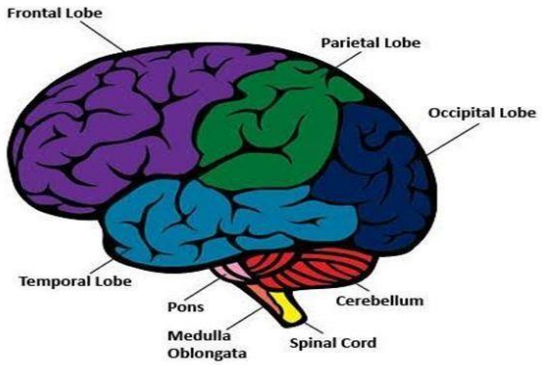

Figure: Parts of Brain [2]

Unfortunately, it is difficult to fully recover from damage to the adult brain because of its limited capacity for self-regeneration. The central nervous system has some capacity for endogenous regeneration, but this is insufficient to guarantee full recovery [1].

Major Types of Stem Cells:

Stem cells have therapeutic significance due to their ability to differentiate under permissive conditions, as well as their anti-inflammatory and immune-modulatory properties. Stem cells can be obtained from different tissues and at any stage of life.

- Embryonic Stem Cells

MeEmbryonic stem cells (ESCs) are derived from the inner mass of blastocysts and can self-renew indefinitely due to their ability to maintain the same phenotype after cell division. ESCs are pluripotent, meaning they can give rise to cells from all three germ layers: the ectoderm, endoderm, and mesoderm. As a result, ESCs can develop into brain cells, providing an almost limitless supply of cells for transplantationuse has significant ethical considerations[22,23].

➢ Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) are terminally differentiated somatic cells that have reverted to pluripotency.Recent research suggests that endogenous production of essential pluripotency factors may facilitate the reprogramming of certain cells. For example, neural stem cells (NSCs) endogenously expressing Sox2 and c-Myc could be transformed by ectopic expression of Oct4 alone[24].

Mechanism:

Overall, stem cells possess distinct features that make them useful in regenerative medicine and the treatment of a variety of diseases and injuries. They are available to differentiate into several cell types, move to injured parts of the body, and release growth factors makes them a viable tool for organ regeneration. After transplantation, stem cells can move and home to damaged parts of the brain, which is attributable to the production of growth factors and chemokines [5]. When stem cells reach the site of injury, they develop into host tissue cells, which replaceinjured and necrotic tissue[6].

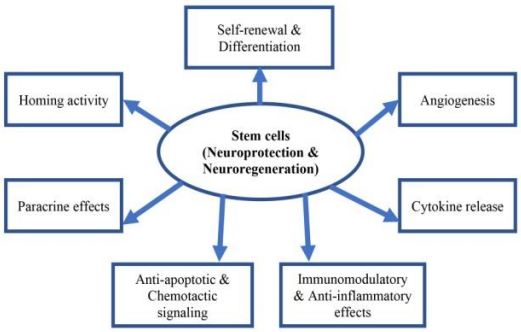

Figure 2: Potential therapeutic actions of stem cells as “neuro-regenerative and or neuroprotective” effect in neurological disorders[6].

The characteristics listed in Figure 2 are critical when contemplating stem cell transplantation for brain injury. Stem cells have the extraordinary ability to self-renew and specialize into many cell types [7]. Stem cells are classified into several types, including neural stem cells (NSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs).

❖ NSCs

primarily originate in the subventricular and sub-granular zones of the hippocampus dentate gyrus. They generate neurons, astrocytes, and oligodendrocytes throughout embryonic central nervous system development [9]. Furthermore, growth agents such as epidermal growth factor[8], fibroblast growth factor-2, and brain-derived neurotrophic factor [10]. can be used to sustain derived neurons in long-term culture.

NSC transplantation therapy are based on these distinct characteristics [9].

❖ ESCs

ESCs are pluripotent cells that can differentiate into all three germ layers, originating from the blastocyst's inner cell mass. As a result, they have been the subject of research as a potential treatment for many neurological illnesses. After transplantation, they can develop into neurons and glial cells [10] and maintain long-term stability, allowing them to integrate with the neurological circuitry [11].

❖ iPSCs

iPSCs are laboratory-engineered cells that mimic ESCs by transforming tissue-specific cells, such as skin cells, into pluripotent cells capable of giving birth to every cell type in the body. While iPSCs and ESCs have many similarities, they are not identical. The effective transformation of somatic cells into iPSCs represents a significant advancement in stem cell and regeneration research.

Routes of administration:

a. Stem Cell via Direct Brain Injection
b. Stem Cells via Intravenous Injection
c. Stem Cells via Intrathecal Injection

a) Stem Cells via Direct Brain Injection

Stem cell therapy via direct brain injection is a promising area of research for treating various neurological disorders Direct brain injection of stem cells involves delivering stem cells directly into the brain tissue through a surgical procedure. This approach aims to promote repair, regeneration, and protection of damaged brain cells[9].

❖ Applications

- Parkinson's disease: Direct brain injection of stem cells has shown promise in preclinical studies for treating Parkinson's disease.
- Huntington's disease: This approach is being explored for treating Huntington's disease, a genetic disorder that causes progressive brain damage.
- Stroke and traumatic brain injury: Direct brain injection of stem cells may help promote recovery and regeneration after stroke or traumatic brain injury.
- Amyotrophic lateral sclerosis (ALS): Researchers are investigating the use of direct brain injection of stem cells for treating ALS.

b) Stem Cells via Intravenous Injection

IV delivery is less intrusive because it avoids the need to make direct access to the central nervous system. Intravenous injection of NSCs can cause localization to ischemic damage sites and allow them to pass through the BBB. In ischemic stroke, IV injection of NSCs, BMMSCs, AD-MSCs or UC-BSCs has demonstrated neuroprotection[9].

c) Stem Cells via Intrathecal Injection

Intrathecal delivery of autologous culture-expanded adipose tissue derived mesenchymal stem cells (AD-MSC) could be utilized to treat traumatic spinal cord injury (SCI) The study's primary outcome was the safety profile, as captured by the nature and frequency of adverse events[9].

Way of Administration:

Preclinical investigations primarily use three types of injection routes: intracutaneous (IC), intraarterial (IA) and intravenous (IV). IC stem cell transplantation appears to be the most effective approach, with the maximum number of cell deposits in the target area of the brain. However, this is the most invasive technique, and studies have shown that stereotactic inoculation of cells might result in haemorrhage or damage (most likely due to needle insertion), fluid loading, neuronal cell death, reactive gliosis, and micro-calcification[12,13].Both intravascular approaches can reduce unwanted brain injury when compared to the invasiveness of the IC treatment. IA treatment has been linked to lower infarct sizes, functional recovery, and a high number of surviving stem cells.

Timing of Stem Cell Administration

Several research have examined various administration times[14]. conducted a trial that supplied stem cells throughout three time periods, beginning 7 days after middle cerebral artery occlusion (MCAo) and ending 28 days later. The stem cells injected 7 days after MCAo performed much better than the cells transplanted at 28 days[14]. Administration 4 weeks after MCAo may thus be too late to be effective [15]. Nam et al. [16] compared one hour, one day, and three days after MCAo injection. The one hour post-MCAo transplanted group demonstrated the best neurological recovery, both functionally and structurally [17].

Dose Of Stem Cells Administered:

Research suggests that a single injection of 3 × 106 cells is more effective than repeated low-dose injections at different periods [18]. The cell concentration-response curve is most likely U-shaped rather than linear, with more cells resulting in a ceiling effect. One study described a severe ipsilateral ocular inflammation, followed by rapid mortality of the examined animals after delivery of 107 cells.

Stem Cell as Therapeutic Approach in Neurological Disorders:

Using stem cells as a treatment for neurological conditions, due to the death of neurons and other central nervous system cells, neurodegeneration causes a progressive decline in brain function[19].When applied therapeutically, stem cells may be able to prevent neuronal degradation and promote the healing of the injured brain's circuitry [20]. The many stem cell types that are employed as treatments for neurological illnesses and disorders will be briefly mentioned in this paragraph, along with some of the potential benefits and issues.

Preconditioning for improved stem cell survival after transplantation:

The uptake and survival of stem cells are hampered by a number of variables, even in spite of the notable progress made in stem cell therapy. Pathological processes, such as local immunological and inflammatory responses, loss of trophic factors, and decreased perfusion and nutrients due to local primary factors responsible for the initial ischemic insult, are responsible for a significant number of donor cell deaths within hours of transplantation [21].

According to earlier research, cytokine priming of cells to a state of "readiness" before to transplantation by activating their survival pathways can strengthen cell engraftment, resulting in increased survival and the resolution of many issues during the post-engraftment phase [25].

Clinical Data and Ongoing Clinical Trials:

184 newborns with acquired neurologic abnormalities participated in a pilot safety trial of autologous cord blood infusion. The short-term safety of intravenous autologous cord blood infusion was bolstered by this retrospective investigation. Numerous randomized controlled trials (RCTs) have been started or will soon publish results utilizing stem cells to treat patients with cerebral palsy, stroke, or newborn HI encephalopathy. In these experiments, there is a great deal of variation in the cell type, the delivery method, and the intervention time. Although there is no preclinical evidence supporting the effectiveness of cell treatment with such a lengthy gap in the juvenile population, cells are often provided weeks to years following the brain injury in most trials[26]. Preliminary data from a Korean clinical trial using rehabilitation, erythropoietin, and allogeneic intravenous stem cell therapy in infants with cerebral palsy aged 2-5 years showed considerable improvement[27].

Future Perspectives of Stem Cells:

The growing body of preclinical research indicates that stem cell treatments for ischemic brain injuries are getting closer to being a practical therapeutic choice. While safety and feasibility of stem cell treatment for stroke have been validated by several phase I clinical studies, more improvements are needed in terms of effectiveness and clinical practicability. These results, applied to human investigations, have given rise to two strategies in clinical trials: acute administration aimed at preventing ischemia harm consequent to stroke, and late administration aimed at boosting neuronal regeneration in the chronic stroke phase [28].

The lack of significant side effects suggests that these cells are safe, yet the study lacked sufficient power to assess functional outcome effects. Thirteen Within 48 hours following an ischemic stroke, a second experiment that used allogenic BMMSCs devoid of CD45/glycophorin. This stands in stark contrast to the abundance of preclinical supportive data for this therapy. Similarly, an openlabel pilot trial on 12 chronic stroke patients showed improved behavioural outcomes 208 weeks after transplant and no immunological effects[29].

The use of stem cells to treat global cerebral ischemia following cardiac arrest is still in the animal research stage of the field, but several studies using rat cardiac arrest models have demonstrated improved neurological and functional results. Inflammatory regulation and BBB integrity preservation are some of the suggested pathways. MSC therapy should be expanded to bigger primate or human models due to the morbidity and mortality of global cerebral ischemia owing to cardiac arrest and the lack of care options to enhance functional outcomes. There aren't any registered clinical studies in this field right now. There are over 55 registered clinical studies examining the impact of several cases [30,31].

CONCLUSION

Over the last few decades, several sources of neuronal regeneration have been investigated. The use of mesenchymal stem cells was also utilized. Various cell sources shown potential, but neural stem cells were found to be particularly effective in targeting and repairing brain injuries. Stem cells treatments are being optimized to overcome difficulties such as targeting the CNS, maintaining therapeutic viability in vivo, and achieving favourable effects without negative repercussions. Continued research, well designed experiments and tissue engineering can help realize the full potential of this innovative technology. Novel techniques, such as intravenous delivery, seem promising and need to be validated in adult primates or humans to fully elucidate their potential for stem cell-based therapies. To further advance this field, methods that combine optimal delivery, dosages, preconditioning and tracking will be needed and should be explored in varying cerebral ischemia models.

REFERENCES

[1] Lindvall O, Kokaia Z. Stem cells for the treatment of neurological disorders. Nature. 2006;441(7097):1094-6.

[2] Gonzales-Portillo B, Lippert T, Nguyen H, Lee JY, Borlongan CV. Hyperbaric oxygen therapy: A new look on treating stroke and traumatic brain injury. Brain Circ. 2019;5(3):101-5.

[3] Sadanandan N, Di Santo S, Widmer HR. Another win for endothelial progenitor cells: Endothelial progenitor cell-derived conditioned medium promotes proliferation and exerts neuroprotection in cultured neuronal progenitor cells. Brain Circ. 2019;5(3):106-11.

[4] Zhang H, Lee JY, Borlongan CV, Tajiri N. A brief physical activity protects against ischemic stroke. Brain Circ. 2019;5(3):112-8.

[5] Verma RS. Breaking dogma for future therapy using stem cell—Where we have reached? Indian J Med Res. 2016;143(2):129-31.

[6] Baraniak PR, McDevitt TC. Stem cell paracrine actions and tissue regeneration. Regen Med. 2010;5(1):121-43.

[7] Ul Hassan A, Hassan G, Rasool Z. Role of stem cells in treatment of neurological disorder. Int J Health Sci. 2009;3(2):227-33.

[8] Ayuso-Sacido A, Moliterno JA, Kratovac S, Kapoor GS, O'Rourke DM, Holland EC, et al. Activated EGFR signaling increases proliferation, survival, and migration and blocks neuronal differentiation in post-natal neural stem cells. J Neurooncol. 2010;97(2):323-37.

[9] Yang CS, He D, Tan J. Co-culture with vascular endothelial progenitor cells: effects on proliferation and apoptosis of neural stem cells and vascular remodeling in rats with ischemia reperfusion injury. Chin J Tissue Eng Res. 2017;21:718-23.

[10] Pincus DW, Keyoung HM, Harrison-Restelli C, Goodman RR, Fraser RA, Edgar M, et al. Fibroblast growth factor-2/brain-derived neurotrophic factor-associated maturation of new neurons generated from adult human subependymal cells. Ann Neurol. 1998;43(4):576-85.

[11] Arnhold S, Lenartz D, Kruttwig K, Klinz FJ, Kolossov E, Hescheler J, et al. GFP labelled ES cell derived neural precursor cells differentiate into Thy-1 positive neurons and glia after transplantation into the striatum of the adult rat striatum. J Neurosurg. 2000;93: 1026-32.

[12] Liu YP, Seçkin H, Izci Y, Du ZW, Yan YP, Başkaya MK. Neuroprotective effects of mesenchymal stem cells derived from human embryonic stem cells in transient focal cerebral ischemia in rats. J Cereb Blood Flow Metab. 2009;29(5):780-91.

[13] Toyoshima A, Yasuhara T, Kameda M, Morimoto J, Takeuchi H, Wang F, et al. Intra-arterial transplantation of allogeneic mesenchymal stem cells mounts neuroprotective effects in a transient ischemic stroke model in rats: analyses of therapeutic time window and its mechanisms. PLoS One. 2015;10:0127302.

[14] Komatsu K, Honmou O, Suzuki J, Houkin K, Hamada H, Kocsis JD. Therapeutic time window of mesenchymal stem cells derived from bone marrow after cerebral ischemia. Brain Res. 2010;1334:84-92.

[15] Stroemer P, Patel S, Hope A, Oliveira C, Pollock K, Sinden J. The neural stem cell line CTX0E03 promotes behavioral recovery and endogenous neurogenesis after experimental stroke in a dose-dependent fashion. Neurorehabil Neural Repair. 2009;23:895–909.

[16] Nam HS, Kwon I, Lee BH, Kim H, Kim J, An S, et al. Effects of mesenchymal stem cell treatment on the expression of matrix metalloproteinases and angiogenesis during ischemic stroke recovery. PLoS One. 2015;10:e0144218.

[17] Bang OY, Lee JS, Lee PH, Lee G. Autologous mesenchymal stem cell transplantation in stroke patients. Ann Neurol. 2005;57(5):874-82.

[18] Omori Y, Honmou O, Harada K, Suzuki J, Houkin K, Kocsis JD. Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats. Brain Res. 2008;1236:30-8.

[19] Peng J, Zeng X. The role of induced pluripotent stem cells in regenerative medicine: neurodegenerative diseases. Stem Cell Res Ther. 2011;2(1):32.

[20] Thompson LH, Björklund A. Reconstruction of brain circuitry by neural transplants generated from pluripotent stem cells. Neurobiol Dis. 2015;79:28-40.

[21] Haider HK. Bone marrow cell therapy and cardiac reparability: better cell characterization will enhance clinical success. Regen Med. 2018;13(5):457-75.

[22] Bjorklund LM, Sanchez-Pernaute R, Chung S, et al. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc Natl Acad Sci U S A. 2002;99(4):2344-9.

[23] Carson CT, Aigner S, Gage FH. Stem cells: the good, bad and barely in control. Nat Med. 2006;12(11):1237-8.

[24] Kim JB, Sebastiano V, Wu G, et al. Oct4-induced pluripotency in adult neural stem cells. Cell. 2009;136(3):411

[25] Tabeshmehr P, Haider HK, Salmannejad M, Sani M, Hosseini SM, Khorraminejad Shiraz MH. Nicorandil potentiates sodium butyrate induced preconditioning of neurons andenhances their survival upon subsequent treatment with H2O2. Transl Neurodegener. 2017;6(1):29.

[26] Sun J, Allison J, McLaughlin C, et al. Differences in quality between privately and publicly banked umbilical cord blood units: a pilot study of autologous cord blood infusion in children with acquired neurologic disorders. Transfusion. 2010;50(9):1980-7.

[27] Allogenic Umbilical Cord Blood and Erythropoietin Combination Therapy for Cerebral Palsy. 2013 [cited 2013 Aug 1]. Available from:

[28] Van Velthoven CT, Kavelaars A, van Bel F, et al. Repeated mesenchymal stem cell treatment after neonatal hypoxia-ischemia has distinct effects on formation and maturation of new neurons and oligodendrocytes leading to restoration of damage, corticospinal motor tract activity, and sensorimotor function. J Neurosci. 2010;30(28):9603–11.

[29] Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, Vallejo-Cremades MT,

[30] Markel TA, Crisostomo PR, Wang M, Herring CM, Meldrum DR. Activation of individual tumour necrosis factor receptors differentially affects stem cell growth factor and cytokine production. Am J Physio Gastrointestinal Liver Physiol. 2007;293(4):G657-62.

[31] Karlupia N, Manley NC, Prasad K, Schäfer R,Steinberg.Intraarterialtransplantation of human umbilical cord blood mononuclear cells is more efficacious and safer than umbilical cord mesenchymal stromal cells in a rodent stroke model. StemCell Res Ther. 2014;5:45.